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RADIATION HAZARDS DURING CHOLANGIOGRAPHIC EXAMINATIONS

by

Kurt Lidén and *Martin Lindgren*

Operative cholangiography has been in use since 1940 at the University Hospital, Lund. It is now a routine measure in the treatment of biliary disease and a standard technique requiring 4 radiographic exposures has been devised (1). The examination is frequently carried out; in 1950, for example, it was employed on about 500 occasions entailing 2,000 exposures. The roentgen intensity necessary for the radiographic examination of the abdomen gives rise to considerable secondary radiation from the patient and thereby exposes the personnel engaged to undue risk.

These radiation hazards were realized and preventive measures adopted. In order to avoid direct irradiation of the operator's hand for instance no exposures are made during the injection of the contrast medium. All personnel attending the operation step a few meters away from the operating table while the films are exposed by a roentgenologist from an adjacent room. Only the anaesthetist is beside the operating table during the exposure and wears a lead-rubber apron; lead-rubber gloves were found to encumber his work and could not be used. A piece of lead-rubber is occasionally placed over the hands and head of the patient during the actual exposure; this has been found to be unsatisfactory as the anaesthetist is unable to watch the patient's face.

As we had no definite idea as to the amount of radiation to which the personnel, particularly the anaesthetist, was exposed, it was decided that the matter should be investigated.

The amount of scattered radiation to which the anaesthetist is exposed will naturally depend upon the stature of the patient and the

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From the Department of Radiation Physics of the University at Lund (Director: KURT LIDÉN) and the Roentgen Diagnostic Department (Director: Professor OLLE OLSSON) of the University Clinics of Lund, Sweden.

varying positions occupied by the anaesthetist from one case to another; it was therefore necessary to study the problem in a fairly large series of cases if representative mean values were to be obtained. Accordingly, some 300 dose measurements at 30 cholangiographic examinations were carried out.

Measuring Technique

The English BD 11 type of ionization chamber, developed and standardised by The Medical Research Council, Radiotherapeutic Research Unit, London, was used. This chamber consists of moulded parts[1] of bakelite graphite in which vanadium oxide is incorporated in order to obtain an air equivalent material (2). The inner electrode is fixed in an insulator made of amber or polystyrene. At our laboratory we have arranged and used about 10 chambers insulated with amber and 50 insulated with polystyrene. The chamber is charged to 250 volts and the readings are made on a Baldwin-Farmer radiologic electrometer. The measuring range is then about 5 to 300 mr. The leakage of the amber insulated chambers is, however, so low that a dose as small as 2—3 mr can be measured.

The BD 11 chambers were packed two at a time in cellophane bags to protect them from moisture and then fastened by means of adhesive plaster to the measuring point: they had, of course, to be calibrated for the quality of radiation being used. From 60 kV, 1 mm Al HVL up to the gamma radiation from Radium B + C the sensitivity increases only about 25—30 per cent. It should also be observed that the half value layer or hardness of scattered radiation is greater than that of the incident beam at 80—90 kV (3), because the softer part of the continuous 90 kV radiation is mainly absorbed as photoelectrons, that is without scatter, while the harder part is partially spread as Compton-photons; the energy of these photons will differ but slightly from that of the primary quanta.

The radiation to which personnel further away from the source of application are exposed was also measured by Victoreen's Minometer chamber, a pocket ionization chamber.

For the measurement in the Roentgen beam we used cylindrical condenser chambers in accordance with the method described by SIEVERT (4).

Radiation Safety Standards

At the International Congress of Radiologists held in London in 1951 the *International Commission on Radiological Protection* recommended a value of 300 mr per week (air dose) as a maximum permissible dose for

[1] Commercially available from Shearex Plastics Ltd., Darlington, England.

those engaged in radiology (5). In Sweden, however, a safety dose of 100 mr has been the rule. No definite information is available about the consequence of occupational irradiation and, in our opinion, the amount of radiation to which the personnel is exposed should therefore be brought down to a minimum.

In the following the term safety dose is to be understood as 100 mr per week.

Risks to which the Operator is Exposed

As mentioned above, no exposures are made during the injection of the contrast medium, and measurements have shown that this would involve unnecessarily great risks. The experimental conditions, which are illustrated in fig. 1, were as follows: A floor stand provided with the necessary measuring instruments was placed at the site which would be occupied by the operator. The irradiated volume corresponding to the size of a patient was built up of suitably shaped wax. In these model tests as many as 20 exposures were made. The measurements showed that if exposures were made during the injection of the contrast medium the unprotected hands (A in fig. 1) of an operator would receive about 5 r during a *single* exposure and the body a surface dose of 10—15 mr.

It is thus obvious that such a procedure is not compatible with radiologic safety. If however, the operator steps a few meters away from the table during the exposure of the film, the risk is diminished considerably. Measurements made during cholangiography showed that a distance of 2—3 meters from the irradiated field is sufficient to bring the irradiation down to safety limits. Details and the results of the measurements are given in the drawing in fig. 2.

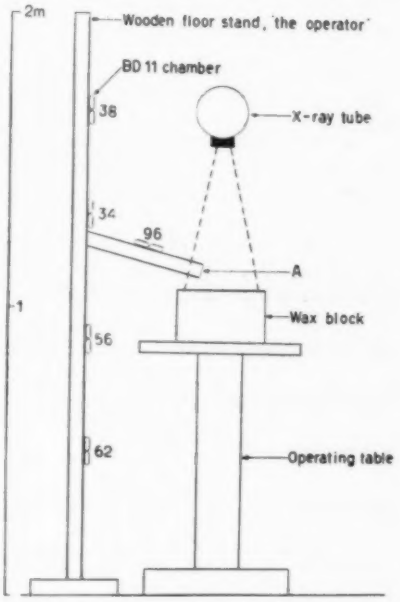

Fig. 1. Model experiment for estimating the amount of secondary radiation to which an unprotected operator is exposed at operative cholangiography. The figures at BD 11 chambers indicate the amount of secondary radiation in mr per cholangiographic examination (4 exposures). At A the average amount measured per exposure was 5 r.

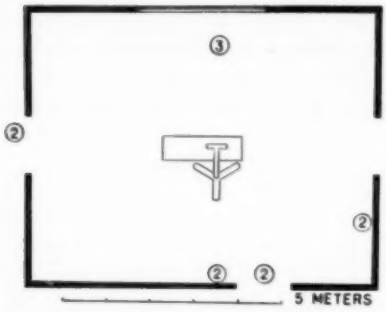

Fig. 2. Sketch of the operating theatre. The rings denote the positions of the members of the staff, and the figures in the rings indicate the doses of secondary radiation measured per cholangiographic examination (4 exposures).

Measurements carried out on attendants a couple of meters from the table showed that they received but little radiation — about 3 mr per cholangiographic examination. As these doses were the smallest that the instruments used could register, it may be assumed that the doses actually received were in reality smaller. Even if the same attendants were present at several cholangiographic examinations a day, the amount of radiation received would be well within the Swedish maximum permissible dose.

Risks to which the Anaesthetist is Exposed

Unfortunately the anaesthetist is unable to leave the operating table during the exposure of the film. The measures described above were therefore taken to afford protection. However, large parts of the body were nevertheless exposed to the radiation, particularly the thorax, neck, head and upper extremities. Irradiation of such a large area is, from the protection point of view, comparable to whole body exposure (5).

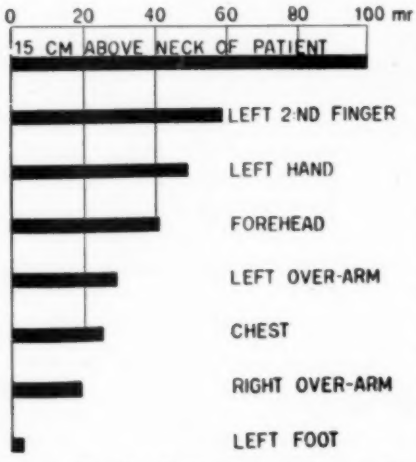

Fig. 3. The distribution of secondary radiation to which an unprotected anaesthetist is exposed during a cholangiographic examination (4 exposures).

In our opinion the anaesthetist was exposed to greater doses than the rest of the personnel and the measurements made confirmed this assumption. By taking measurements at a large number of points we received an accurate picture of the distribution of the doses received. A study of the results showed that the spread of the measured values at a given point was considerable. This is due to the various working positions assumed by the anaesthetist and to the different

thicknesses of the volume irradiated, both of which depend upon the stature of the patient. The average dose received at certain points during a single cholangiographic examination is given in fig. 3.

As an example of the total spread it may be mentioned that values between 25 and 115 mr were measured on the left hand and between 20 and 80 mr on the forehead.

As the number of cholangiographic examinations per anaesthetist per year at Lund is about 150, he would, if unprotected, receive 6,000—10,000 mr at those sites exposed most, *i. e.* a value exceeding the Swedish maximum permissible dose.

When assessing the risks to which the anaesthetist is exposed, the additional radiation energy received, for example, during angiocardiography must be taken into account.

Protective Measures

It was therefore necessary to provide some sort of protection; the arrangement should as far as possible give the anaesthetist protection against scattered radiation and at the same time not encumber his movements or view of the operation field. Moreover, it should be simple in design and not disturb the work of the operator.

The protective arrangement devised is similar to that used by ENGESET in cerebral angiography (6). It consists of a lead-rubber shield (lead equivalent 1.2 mm) provided with a lead-glass window (13 × 18 cm). The lower third of the screen is divided into three overlapping parts so that the lead-rubber screen may accommodate itself to the shape of the chest. In our investigation the frame was fixed to a mobile floor stand.

The effectiveness of the protective shield[1] was checked. A few wax blocks represented the patient and a person *not* employed in radiologic work was placed in the position normally occupied by the anaesthetist. The usual measurements were made on this individual as he stood in the same position during 20 exposures, corresponding to 5 cholangiographic examinations. The radiation to which he was exposed was measured at ten different points of the body. No measurable amounts of radiation could be registered. Measurements on the model of surface dose in the incident beam showed *15—20 r per 4 exposures.*

The manner in which the anaesthetist works with this new protective shield is illustrated in fig. 4, which shows the shield in position during cholangiography. The lead-rubber shield is lowered on the non-sterile side of the screen. The anaesthetist is now able to follow the respiratory movements of the patient through the lead-glass window. Clinical experience has shown that this screen does not disturb the work of the

[1] Manufactured by *AB Svensk Röntgen*, Malmö, Sweden.

Fig. 4. Protective shield for anaesthetist in use during operative cholangiography.

operator. The duties of the anaesthetist are unhindered because neither a lead-rubber apron nor any other protection is necessary.

The measurements made thus show that up to now the anaesthetist has been exposed to undue risks during cholangiography as performed so frequently at Lund. However, since the introduction of the protective shield these risks for the anaesthetist have been completely eliminated. *In this way operative cholangiography is now, from the radiation protection point of view, free from any hazards.*

This investigation has been supported by a grant from *the Swedish Medical Research Council.*

SUMMARY

In Sweden the radiologic safety dose is taken as 100 milliroentgens per week. Radiation measurements during cholangiographic examinations at Lund showed that all assistants standing 3 meters from the irradiated field received such a small amount of radiation that no special protective measures were necessary. The upper part of the anaesthetist's body however was found to be exposed to considerable amounts of radiation.

A protective lead-rubber shield with a lead-glass window was therefore designed and control measurements showed that it completely fulfilled its purpose of absorbing the scattered radiation.

ZUSAMMENFASSUNG

Die höchst zulässige Toleranzdosis für radiologisch tätige Personalgruppen beträgt in Schweden 100 Milliröntgen per Woche. Strahlungsmessungen bei Cholangiographien in Lund ergaben, dass besondere Strahlenschutzanordnungen für Personal in mindestens 3 Meter Entfernung vom Operationsgebiet nicht notwendig waren. Der Narkotisör jedoch empfing beträchtliche Strahlenmengen gegen die oberen Körperpartien.

Die Konstruktion einer Strahlenschutzanordnung aus Bleigummi, versehen mit Bleiglasfenster, war die Folge. Kontrollmessungen zeigten, dass der Narkotisör nunmehr keinerlei messbarer Sekundärstrahlung ausgesetzt war.

RÉSUMÉ

La dose de tolérance admise en Suède est de 100 milli r par semaine. Des mesures effectuées pendant des examens cholangiographiques à Lund ont montré que les assistants se tenant à 3 mètres du champ irradié recevaient des doses de rayonnement assez faibles pour qu'aucune mesure spéciale de protection ne soit nécessaire. Au contraire, le haut du corps de l'anesthésiste était exposé à des doses considérables de rayonnement.

C'est pourquoi on fit faire un écran protecteur de caoutchouc plombé, muni d'une fenêtre de verre au plomb; des mesures de contrôle ont montré qu'il remplissait parfaitement sa fonction de protection contre les radiations diffusées.

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FROM THE 1ST ROENTGEN DEPARTMENT (DIRECTOR: GUNNAR JÖNSSON), SÖDERSJUKHUSET, STOCKHOLM, SWEDEN

INFUNDIBULUM OF PATENT DUCTUS ARTERIOSUS — A DIAGNOSTIC SIGN IN CONVENTIONAL ROENTGENOGRAMS

by

Gunnar Jönsson and *Georg-Fredrik Saltzman*

Now that it has proved possible to close a patent ductus arteriosus by surgical intervention and thus to prevent the dangerous complications of heart failure and bacterial endocarditis, definite and early diagnosis becomes a matter of vital importance. In many cases the anomaly can be diagnosed with a high degree of certainty from the murmur characteristic of patent ductus arteriosus. This is often absent, however. ABBOTT, for instance, has pointed out that the typical continuous murmur is present in only one-third of all cases.

During the past few years, two other methods by which the certain diagnosis of patent ductus arteriosus can be made have become available. If, in connection with heart catheterization, the catheter can be passed from the pulmonary artery, through the ductus and into the aorta (KARNELL, JÖNSSON and BRODÉN, ALVAREZ, LIMON LASON and BOUCHARD) the diagnosis is established beyond all doubt. This is only possible, however, where the ductus arteriosus is wide. With the aid of thoracic aortography a diagnosis can be made with great certainty irrespective of the width of the ductus (JÖNSSON, BRODÉN, HANSON and KARNELL, BURFORD and CARSON). However, one of the conditions for the adoption of these methods is that signs and symptoms justifying the performance of these delicate and time-consuming examinations should be present. In those cases where no suggestive auscultatory signs are found we must rely on conventional roentgenograms.

Enlargement of the heart, dilatation of the pulmonary artery, and the pathologic pulsations in the central branches of the pulmonary artery known under the name of hilar dance have long been on record as char-

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acteristic roentgenologic features of patent ductus arteriosus. These signs are common in patent ductus, but they are neither constant nor specific findings. The commonest of them, dilatation of the pulmonary artery, is demonstrable in 50—75 per cent of all cases. However, these changes are only to be regarded as a secondary phenomenon to a left-to-right shunt, and are encountered to a greater or lesser degree in all forms of this type of shunt. The only pathognomonic lesion visible on conventional roentgenograms, as yet described in connection with patent ductus arteriosus, is calcium deposits in the ductus. These are fairly rare, however. Among our 39 cases of patent ductus arteriosus, only 2 had roentgenologically demonstrable calcifications in the ductus.

During our investigations into patent ductus arteriosus with the aid of thoracic aortography the possibility of seeing the infundibulum of the ductus on conventional roentgenograms began to occupy our thoughts. It was hoped that we might find a more or less pathognomonic sign that would be demonstrable at a simple routine examination.

Our work in connection with thoracic aortography had shown that the infundibulum of the ductus is usually seen best on lateral views. Unfortunately, conventional lateral views are not suitable for the study of the anatomy of the aorta, at least not with the age-classes in question. In the two cases we have described, in which the uppermost part of the descending aorta was uniformly widened, the anomaly was, however, clearly visible on conventional lateral views.

In most of the cases examined by thoracic aortography, the infundibulum of the patent ductus was also visible in A. P. views. We therefore concentrated our studies to the appearance of the aorta on conventional P. A. views. It was found that in a great many cases a deformation could be seen in the outline of the aorta in the situation where the aortic arch (the »aortic knob») becomes continuous with the descending aorta (fig. 1). Of 39 cases of patent ductus arteriosus (in 27 cases the diagnosis was made with the aid of thoracic aortography or catheterization of the ductus; in 12 cases it was verified at operation or necropsy) 21 showed definite deformation of the aortic shadow at the site of the infundibulum of the ductus. A possible deformation was suspected in 5 cases, and in 13 cases no change was distinguishable. Thus, definite malformation of the aorta at the site of the ductus arteriosus was observed in slightly more than one-half of the total.

In the majority of the cases the concavity normally present on the left side of the aorta, in the region where the arch passes over into the descending aorta, was lacking; it was replaced by a slight convexity which gradually became continuous with the straight outline of the descending aorta (figs. 1—2). The impression gained was that the point of transition between the aortic arch and the descending aorta was

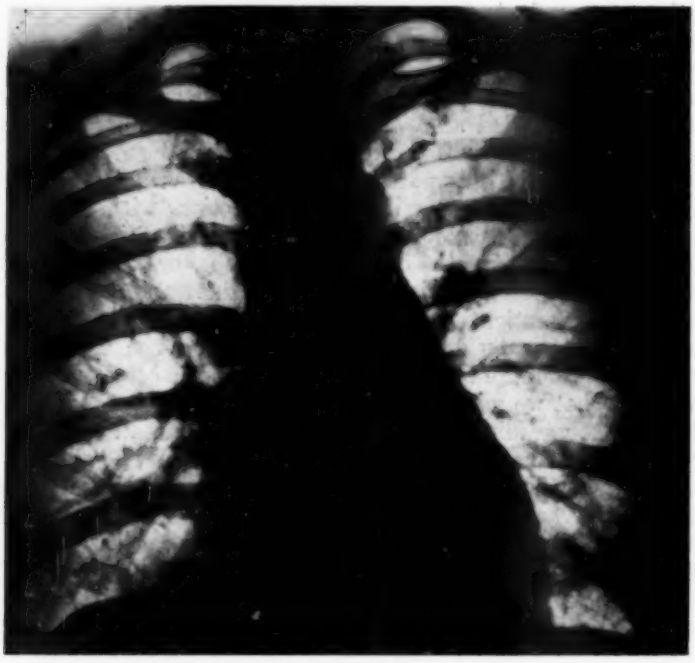
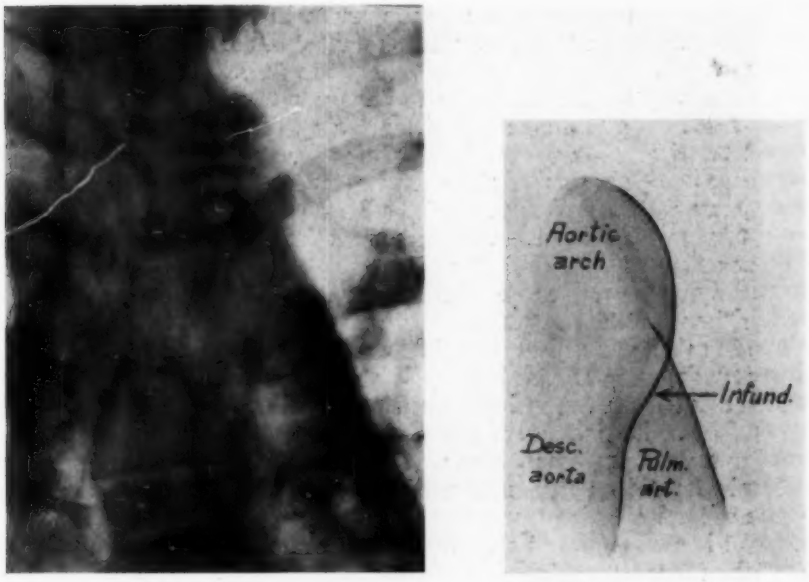


Fig. 1. Survey view in a case of patent ductus arteriosus with characteristic deformation of the aorta.

displaced downwards. Only in a very few cases we were able to see in the conventional roentgenograms a bulge short and distinct enough to make us feel that we were looking at the actual infundibulum. In most instances, there was a marked difference between the contrast shadow produced in connection with thoracic aortography and the aorta outline on conventional roentgenograms from the same case. This can readily be understood. In the aortographic examination, the inner wall of the aorta is outlined whereas the conventional roentgenogram furnishes information regarding the outer contour only and then merely indirectly. The outline visualized is the border between the aerated lung parenchyma and the pleura. A thin layer of mediastinal tissue also lies between the pleura and the aorta. To a certain extent, this fills out irregularities in the aortic outline, and these are consequently not brought into fully detailed relief. We have been able to observe in several aortographies that the space usually present between the aortic arch and the bulge caused by the infundibulum was filled with mediastinal tissue (fig. 3).



a. b.

Fig. 2. Detail view of the same case as in fig. 1. The point where the aortic arch passes over into the descending aorta seems to be displaced downwards.

Cases are not infrequently encountered in which the aortic outline is difficult to distinguish in the situation where the aortic arch changes into the descending aorta; in a number of cases, the outline of the aorta is lost in the shadow of a distended pulmonary artery. The contours of the aorta in some of these cases, however, can be traced downwards for a sufficient distance to enable it to be established that the aorta must be deformed in the characteristic manner described above.

Conventional P. A. views were made in all our cases with the patient standing erect, the greatest care being taken to ensure that the chest was perfectly straight. Taking into consideration the fact that in most cases the ductus arteriosus does not arise from the centre of the anterior wall of the aorta but slightly to the left of the centre, the examination has been supplemented during the past year with films taken with the patient's left shoulder drawn slightly backwards. This measure has resulted, in some instances, in films in which the bulge caused by the infundibulum is more clearly visualized. We have not succeeded by this means, however, in visualizing an infundibulum deformity not already visible on a straight P. A. view.

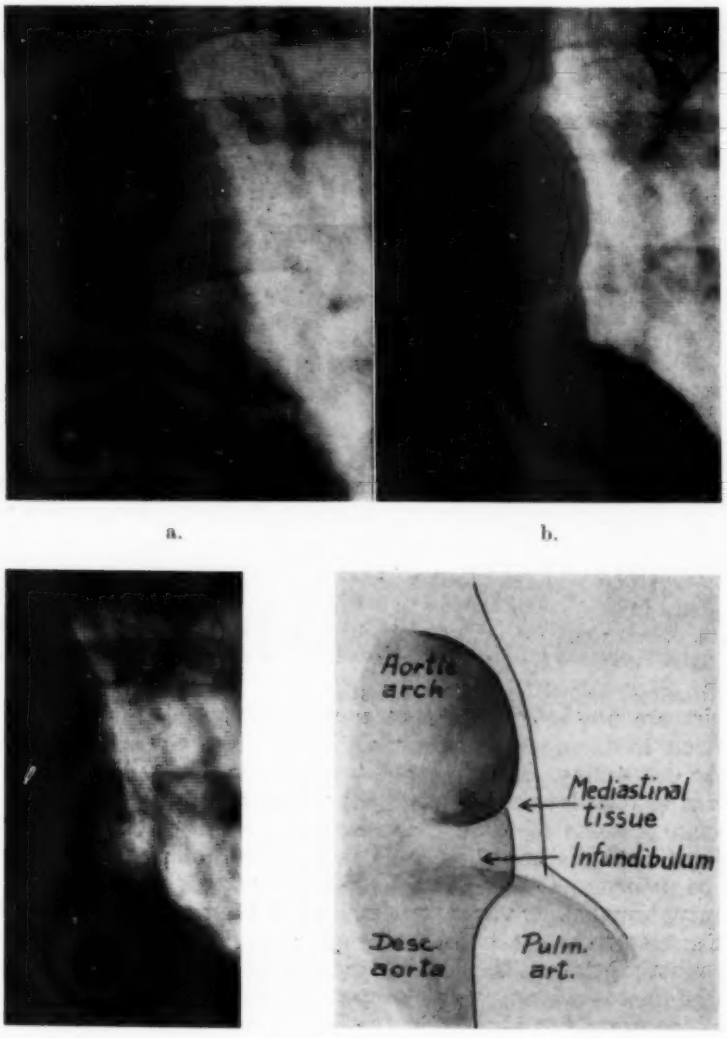


Fig. 3. a. Conventional roentgenogram. There is a slight convexity of the left mediastinal outline against the lung just below the aortic arch. It is of the same type as in figs. 1 and 2 and indicates the presence of a patent ductus arteriosus.

b—d. Thoracic aortogram. The lumen of the aortic arch and the infundibulum of the patent ductus is distinctly seen (b). The periaortic tissue hides details in the outer contours of the vessel; the outline is therefore shown as an even, convex line (c and d).

As mentioned before the deformation was not visualized in 13 cases. The reason in most of these cases was that a greatly distended pulmonary artery almost entirely concealed the uppermost part of the aorta (4 cases). In the face of such a distention the shadow of the aorta is too poor to allow its outlines to be studied. In other cases, the conditions in the aorta could not be interpreted owing to thorax deformity (2 cases). Even when the aortic outlines can be distinguished the greatest caution should be exercised in interpreting the appearances, since it has been demonstrated that the anatomy and topography of the intrathoracic soft tissues are often altered when deformity of the thorax is present. The mutual relations of the great vessels are subject to certain variations even in a normal thorax. In those cases where the ductus arteriosus runs in a dorsal-ventral direction and arises in the centre of the anterior wall of the aorta it is sometimes impossible to distinguish infundibulum deformities on conventional P. A. views, especially when the infundibulum is relatively small (1 case). In these cases, the infundibulum is as a rule very poorly visualized even on A. P. views produced during thoracic aortography. The anatomy of the aorta undergoes considerable changes in elderly persons. It is probably quite impossible in many cases to distinguish between a deformity due to age and one caused by the infundibulum of a patent ductus arteriosus on P. A. views. However, the diagnosis of a patent ductus in patients of an age when such a confusion could arise seldom comes into question. Finally, it is obvious that we should not have seen a deformation of the aortic shadow on the conventional roentgenograms in the two cases in which no infundibulum at all could be demonstrated at the thoracic aortographic examination. Nor was it possible to see such a deformity in the case where the ductus arteriosus arose almost from the very middle of the aortic arch. The infundibulum of the ductus in this patient was only visible on lateral views obtained during thoracic aortography. In 3 cases only, no plausible explanation could be found to explain why the deformity in the aortic shadow characteristic of a ductus infundibulum was not visible on the conventional roentgenograms.

In all the cases on which these observations are based, the patent ductus arteriosus was the only congenital anomaly in the heart and great vessels. We have encountered 12 cases in which a patent ductus was present in conjunction with coarctation of the aorta. The aorta is so much changed and the anatomy varies so considerably from case to case in patients of this kind that it is not possible to make any study with a view to demonstrating the possible existence of a ductus infundibulum. Cases in which a patent ductus arteriosus was found in combination with other congenital anomalies have been too few to permit of any conclusions being drawn.

Can a deformity of the aortic shadow similar to that described be present in normal cases? In order to find an answer we examined 50 physically healthy subjects with the special aim of demonstrating the possible existence of a typical deformation of the aorta. The majority of these subjects were mentally ill patients who had been sent to hospital for a routine examination of the heart before electro-shock treatment. These investigations were carried out only in young persons in whom there could be no question of there being any changes in the aorta due to age. In one instance, we observed a suspicious-looking deformation in the aorta at the typical site. However, a careful clinical examination revealed that this patient had a weak systolic murmur as well as an accentuated P II. Since our interest in the appearance of the aorta shadow in patent ductus arteriosus was first aroused we have, furthermore, kept this feature of the roentgenogram more or less in mind in all the thousands of thorax investigations that have been carried out in the department during the past year. We have during this time encountered two more cases where deformation of the aortic shadow was suspected. In one of these cases, also, a systolic murmur was heard, in the other no pathologic findings were recorded at the clinical examination. These three patients had no subjective symptoms and a control examination with the aid of thoracic aortography was therefore not considered to be warranted. As has already been mentioned, a definite, typical deformation in the outline of the aorta at the point where the aortic arch passes over into the descending aorta was observed in 21 out of 39 patients with patent ductus arteriosus. We have not seen such a pronounced deformity in any patient who did not have an established patent ductus arteriosus.

The observations described are based almost exclusively on investigations carried out on adults. Through the courtesy of Dr. F. ULFSPARRE, of Crown Princess Lovisa's Hospital for Sick Children we were given the opportunity of studying the hospital's large series of cases of patent ductus arteriosus verified at operation. We found that an irregularity in the aortic shadow typical of the infundibulum was also distinguishable in a great many of these children although not in as many as among the adults. In the case of children, there are several additional factors that make it difficult to interpret the roentgenograms. It is very difficult to obtain absolutely straight P. A. views when dealing with small lively children. Many of the smallest children have a large thymus that covers the upper part of the aorta, thus making it impossible to study the requisite portion of the aortic shadow.

It would appear that a deformation in the outline of the aorta could be a common and, in practice, a specific finding in conventional P. A. roentgenograms in patent ductus arteriosus.

Since this article was submitted for publication we have encountered a case without a patent ductus arteriosus, in which the aorta was deformed in the conventional radiogram. The deformity was, however, situated slightly higher up in relationship to the pulmonary artery than in our cases with patent ductus arteriosus. Aside from a systolic murmur, no pathologic changes in the circulatory organs, lungs or skeleton of the thorax were found on clinical or radiographic examination. Thoracic aortography revealed that the upper part of the aorta was atypical. On the other hand, there was no infundibulum that could furnish an explanation of the appearance of the aorta in the conventional radiogram.

This case illustrates the importance of observing the position of a suspicious aortic deformity in relationship to the pulmonary artery; if an aortic abnormality of this kind be due to an infundibulum of a patent ductus arteriosus it is always projected against the pulmonary artery in the P. A. views. It was unlikely therefore that a patent ductus was present, since the pulmonary artery was situated too low down in relationship to the aortic deformity.

SUMMARY

In a series of 39 cases of patent ductus arteriosus, a deformity of the outline of the aorta characteristic of the infundibulum of the ductus was demonstrated in 21 cases in conventional true P. A. roentgenograms. This aortic irregularity was not observed in comparative studies on a series of normal subjects. A possible infundibulum deformity cannot be demonstrated in cases in which certain types of thorax deformity are present or in which there are certain divergences from the ordinary anatomy and topography of the intrathoracic soft tissues; nor can it be demonstrated when the pulmonary artery is greatly distended, or in children with large thymi.

ZUSAMMENFASSUNG

In einer Serie von 39 Fällen mit offenem Ductus arteriosus wurde eine Deformierung der Aussenkontur der Aorta, die charakteristisch für das Infundibulum des Ductus ist, in 21 Fällen auf üblichen p. a. Röntgenbildern demonstriert. Diese Unregelmässigkeit der Aorta wurde bei vergleichenden Studien an einer Reihe von Gesunden nicht beobachtet. Eine etwaige Deformität des Infundibulum kann in Fällen mit gewissen Typen von Thoraxdeformierungen und in Fällen mit gewissen Abweichungen von der üblichen Anatomie und Topographie der intrathorakalen Weichteile nicht dargestellt werden; auch ist sie bei einer stark erweiterten Pulmonalarterie oder bei Kindern mit grosser Thymus nicht nachweisbar.

RÉSUMÉ

Dans une série composée de 39 cas de persistance du canal artériel on a observé une déformation du profil extérieur de l'aorte, dans 21 cas. Cette déformation est caractéristique de l'infundibulum du canal artériel sur les radiogrammes conventionels postéro-antérieurs. La déformation de l'aorte n'a pu être constatée lors d'études comparatives sur une série de sujets normaux. La déformation infundibulaire ne peut pas être

révélée chez les sujets atteints de certains types de difformités thoraciques ou chez lesquels il y a certaines anomalies de l'anatomie et de la topographie des organes intrathoraciques. Elle est également invisible dans les cas où l'artère pulmonaire est fortement distendue ou chez les enfants à grand thymus.

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FROM THE DEPARTMENT OF ROENTGENOLOGY, AMERICAN UNIVERSITY OF BEIRUT, LEBANON

FAMILIAL AND SPORADIC NEUROGENIC ACRO-OSTEOLYSIS

by

L. Giaccai

Chronic perforating ulcers of the extremities associated with changes in the underlying bone structures are of common occurrence in virtually any lesion of the nervous system causing abolition or impairment of sensory function. Though the pathogenesis of neurotrophic ulcers and osteoarthropathies is not clear, especially regarding the enigmatic »trophic effect» of nerves, most disturbances may be considered as symptomatic of an underlying nervous disease *i. e.* tabes dorsalis, syringomyelia, spinal cord tumors, etc.

In addition to these »symptomatic» forms, there is a group of presumably neurogenic osteopathies which in the present state of our knowledge, may be considered as »essential»; the lesions of the soft tissues and bones, though associated with sensory disturbances, appear as the primary and most outstanding feature of the disease, because the nature of the lesions of the sensory tracts is unknown. We may distinguish two types of essential neurogenic osteopathies, the one occurring with a familial incidence and the other sporadically. The two types, though fundamentally akin, differ from each other in certain clinical and roentgenologic characteristics, and will therefore be treated separately.

Familial Neurogenic Acro-Osteolysis]

This condition is characterized by chronic ulceration resulting in extensive mutilation of the feet, sensory disturbances of the extremities and a familial incidence. It has gradually become more definitely classified as the number of cases in the medical literature have increased. Sixty-eight typical cases have been reported but as the condition is a

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familial one, the number rises to 129 if we include members of the patient's families who were stated to have been affected by the disease.

Symptoms and Signs. The condition has a definite familial incidence and more than one successive generation may be involved. Males are affected more frequently than females, the ratio being about 3 to 1. The disease usually begins in childhood or early adolescence. A slightly painful area of ulceration makes its appearance on the plantar aspect of the foot, following what is described as a »swelling» or a »blister». After some weeks or months, during which time the ulcer grows slowly in size and depth and discharges, a bony spicula is eliminated and the ulcer heals. After an interval of a few weeks or months, a swelling appears in the same, or in another, region of the sole and ulceration again occurs; this continues to discharge until one or more bone fragments are expelled. Some months or a few years after the initial ulcer, similar changes commence in the other foot. The disease progresses thus with more or less frequent relapses; as a rule, whenever a new swelling appears, the temperature rises (38°—39°) but drops as soon as the discharge commences. The fever, which lasts a few days, is associated with an enlargement of the inguinal glands. The feet become deformed, chronically swollen and extensively mutilated. The general condition is unaffected and the patients can usually walk, although with difficulty, without pain.

Sensory disturbances are always associated with the lesions of the feet. Superficial sensibility is more or less impaired, the sensation of pain being usually the most affected, followed by those of heat and touch. In no typical case is a clear-cut syringomyelic dissociation encountered. Sensory impairment is most pronounced distally and is not so marked at higher levels in the legs. Deep sensations are usually either intact or slightly decreased. The tendon reflexes of the lower limbs are usually preserved but in advanced cases may be diminished or even abolished. The upper extremities frequently show the same symmetrical sensory disturbances as the lower limbs, although usually to a lesser degree.

The prognosis quoad valetudinem is unfavorable and no treatment has so far succeeded in arresting or slowing down the progressive course of the disease. The prognosis quoad vitam is fair and no case of death due to complications directly arising from the disease has been so far reported.

Roentgen appearances. The bone changes characteristic of familial acro-osteolysis are found to be almost always complicated by superadded chronic osteomyelitis involving the bone in the region of the ulceration. As the ulcers are mostly situated on the plantar aspect of the foot corresponding to the heads of the first or second metatarsal bones, the osteomyelitic changes firstly appear in these regions. They consist of a varying

degree of irregular bone rarefaction, sclerosis and destruction, with the formation of sequestra, followed by progressive fragmentation of the shaft and distal epiphysis.

Changes typical of familial acro-osteolysis are of a quite another type and are most evident in the phalangeal bones where as a rule they may appear, uncomplicated by osteomyelitis. The changes are essentially of the osteolytic type and show the general pattern of so called »concentric bone atrophy». The shafts are thinned out towards the epiphyses which remain unaffected until the late stages. When the shafts have been completely destroyed, the epiphyses remain as loose bone fragments which either undergo slow reabsorption or are eliminated as sequestra.

The bones undergoing progressive destruction show no evidence of reactive changes. The joints are conspicuously unaffected; even when the destructive process has extended towards the epiphyses, the corresponding interphalangeal joints remain of normal width and the articular surfaces perfectly regular.

The bone changes are generally more pronounced on the distal and medial aspects of the foot, although the bone destruction gradually extends proximally and laterally to involve the metatarsal bones. The tarsal bones, unless the site of osteomyelitis, show only a moderate degree of decalcification; the ankle joints are unaffected.

Etio-Pathogenesis. No autopsy finding had so far been reported and therefore the etio-pathogenesis had been discussed only on a clinical basis. A certain resemblance between this condition and syringomyelia has caused most authors to regard it as a special form of the latter disease. In 1883, MORVAN (13) described 7 cases of a new syndrome observed among the fishermen of Brittany and characterized by analgesic whitlows of the hands resulting in mutilated phalanges. MORVAN held the view that the condition was due to a lesion of the spinal cord of a syringomyelic type. MORVAN's cases had no familial occurrence. On the other hand, familial incidence in syringomyelia had been repeatedly observed and when the first few cases of familial »neurotrophic» injuries of the feet were reported, »Morvan's disease» and »familial syringomyelia» became associated in a syndrome known as »Morvan's type of lumbo-sacral syringomyelia» or »familial lumbosacral syringomyelia».

Under the terms »myelodysplasia» (FUCHS, 9) and later »status dysraphicus» (BREMER, 4), further observations on familial neurogenic acro-osteolysis were ascribed to development malformations of the neuro-spinal axis related to dysraphism.

At present, this rare condition is described by most authors as being in the nature of lumbo-sacral syringomyelia or spinal dysraphism with myelodysplasia; it is also referred to as »familial neurotrophic osseous

Figs. 1—3. Case 1 (Su.), case 2 (Sa.), case 3 (Si.). Thickening of the soft tissues. Torpid ulcerations of the feet.

atrophy» (18), »familial trophoneurosis», and acropathie ulcéro-mutilante (19).

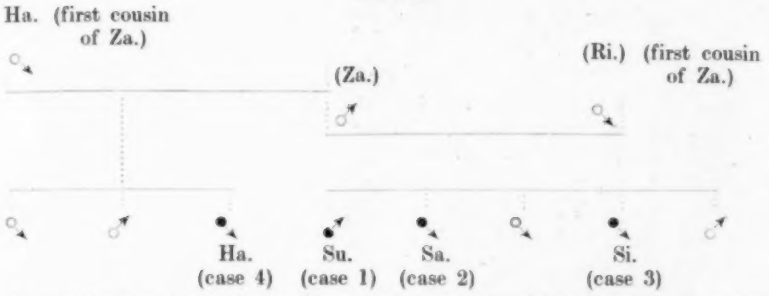
The *Case reports* cover four Arab out-patients. There was no family history of any disease involving the feet or nervous system. The father of the four patients had married twice, on each occasion a cousin (table I). Of the three children of the first marriage one developed ulceration followed by mutilation of the feet at the age of 13; she died at the age of 35 of aplastic anemia. Of the five children of the second marriage, the first, second and fourth developed familial acro-osteolysis between the age of 7 and 13.

The clinical histories of the four patients were typical and consisted of torpid ulceration of the feet with the discharge of sloughy material and bone sequestra, progressive thickening of the soft tissues of the feet and progressive destruction of the toes (fig. 1, 2, 3). Loss of sensation in the feet gradually developed, extended to the hands and included loss of tactile sense.

The neurologic signs were similar in all the four cases, heat, pain and tactile sensations were markedly impaired or abolished from the feet to the middle of the legs. Position and vibration sense was absent at the toes and decreased at the knees. In the upper limbs, heat, pain and tactile sensations were intact but there was decreased position and vibration sense with asteregnosis. The ankle- and knee-jerks were either diminished or absent; the triceps, biceps and radio-brachialis tendon reflexes were either decreased or abolished. The motor system was intact and the cranial nerves normal.

Case 2 was admitted to hospital. A culture of a scraping from the ulcer of the foot was negative for fungi and t. b. bacilli; a culture of

Table I



I. Family: the block signs indicate the siblings affected by familial neurogenic acro-osteolysis.

the discharge gave no growth of aerobic or anaerobic organisms. W. R.: negative. Oscillometry: lower limbs: moderate decreases with a maximum of 2 divisions at the mid-thigh and a maximum of 1 division at the mid-leg at 150 mm. Hg; upper limbs: maximum oscillations, 2 divisions at 150 mm. Hg; forearms: $1^1/_2$ division at 150 mm.

A post-mortem examination of *Case 4* was performed. The whole spinal cord, the nerve roots and the meninges presented normal macroscopic appearances. Sections taken at different levels of the cord and examined microscopically, failed to reveal any changes.

Roentgen appearances. (Fig. 4, 5, 6.) These are constant in all cases although the amount of bone destruction varies. Osteomyelitic changes, with destruction of the first metatarsal bones and involvement of the other metatarsals, are seen. Changes characteristic of acro-osteolysis are shown in the distal segments of the feet. The distal phalanges have almost completely disappeared, the mid-phalanges are mostly reduced to small

Fig. 4. Case 1 (Su.) Osteomyelitic changes in metatarsal bones and phalanges.

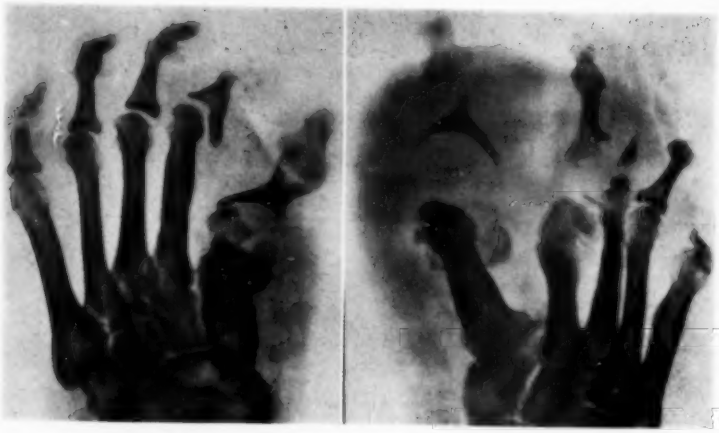


Fig. 5. Case 2 (Sa.) Similar changes as in case 1.

Fig. 6. Case 3 (Si.) Stump of the shaft of the 2nd metatarsal bone. The pencil point appearance is characteristic.

stumps and the proximal phalanges as well as the metatarsal bones show different degrees of concentric atrophy. In case 3 (Fig. 6), the stump of the shaft of the second metatarsal bone of the left foot has a characteristic candle-stick or pencil-point appearance. The bone changes show a definite symmetry in all the cases and are most marked in the medial and distal parts of the feet. Roentgen examinations of the spine revealed: in Case 1, a lumbo-sacral vertebra of a transitional but symmetrical type; in Case 2, sacralization of the

fifth lumbar vertebra on the right side and a difference in the length of the twelfth ribs. The corresponding vertebra was of a transitional dorsi-lumbar type; in Case 3 no abnormality. The last case (4) could not be examined. No changes were discovered in the hands although the patients complained of long-standing sensory disturbances.

Sporadic Neurogenic Acro-Osteolysis

The non-familial type of neurogenic acro-osteolysis is possibly much more common than the familial; since, however, the signs are not so striking as in the familial type it is apt to be wrongly diagnosed as »chronic osteomylitis», »tuberculous osteitis» or »trophic ulceration of the foot». I believe that this is the reason why the number of cases reported are fewer than the cases of familial acro-osteolysis; the familial incidence and the symmetrical mutilations draw attention to the latter condition.

Thirty-three typical cases are reported in the literature; 21 of these are collected in a paper by KIENBÖCK (11), under the title of »Trophopathia pedis myelodysplastica».

Besides being non-familial, sporadic acro-osteolysis differs from the familial type in the following characters: 1) It is often unilateral. 2) The sensory disturbances of the foot are inconstant and if present, are usually not so conspicuous. 3) It is almost always associated with demonstrable malformations of the spine and of the foot. 4) There is no definite sex incidence [18 males and 15 females in the cases reported]. 5) The progress of the disease is more rapid; within a few years the maximum degree of mutilation is reached and the condition then becomes stationary, save for occasional relapses.

In other respects the clinical features of sporadic acro-osteolysis do not differ from those of the familial type. They also appear at an early age. Recurring ulcers and elimination of sequestra mark the progress of the disease until extensive mutilation of the foot results. Sensory impairment is an inconstant feature; when present, it is usually confined to the affected foot. As in the familial type, superficial sensation (pain, touch and thermic) is more affected than deep sensation. In none of the reported cases was there impairment of sensation in the upper limbs.

As the disease is as a rule associated with congenital or developmental deformities of the foot, such as talipes varus, equinus, flat-foot, etc., the situation of the ulceration varies and the changes due to osteomyelitis will involve the bone structures on which the body weight is mostly borne. Thus, we find that in talipes varus, the lateral metatarsals are extensively involved or destroyed by osteomyelitis, whereas in the condition of club-foot the distal bones will show the more advanced changes. As to the characteristic osseous changes, they are of the same

Fig. 7. Case 5. Right foot: Large ulceration on the lateral side; the toes missing.

type as in the familial form; concentric bone atrophy is the basic change and is most marked in the distal part of the foot.

Etio-Pathogenesis. As in familial acro-osteolysis, the etio-pathogenetic problem of the sporadic type has been argued on a clinical basis. KIENBÖCK (11) in 1930 reviewed 17 cases previously reported, to which he added 4 of his own cases and named the condition »Trophopathia pedis myelodysplastica». Spina bifida or more marked malformations of the spine, congenital malformations of the foot, etc., are of much more common occurrence in the non-hereditary, non-familial type, but the occasional finding of sensory disturbances prompted KIENBÖCK to describe the condition as related to myelodysplasia, which is often associated with malformations of the spine. Other authors hold the view that this condition is also due to a special form of syringomyelia (lumbosacral type). The fact that in almost all the reported cases, the lesions of the foot were associated with demonstrable dysplastic abnormalities of the spine, corroborates KIENBÖCK's assumption.

The following case appears to confirm these theories.

Case report. An Arab girl, aged 18, upon examination had gross deformity and advanced mutilation of the feet. The toes of the right foot were missing (Fig. 7) and there was a large, shallow, oozing area of ulceration on the lateral side of the sole. The little toe of the left foot had disappeared, the other toes being plump, stumpy with old scars at the extremities and on the plantar aspects. There was nothing of interest in the family history. 3 brothers and 3 sisters were living and well. The patient was born with talipes equino-varus of the right and talipes equino-valgus of the left side, for which she had to wear special boots in infancy. Swelling and ulceration of both feet started at the age of 2 years and often recurred, after temporary healing, until the age of 8 years; the mutilation then developed and the condition became stationary.

Neurologic examination: The sensations of touch, pain and temperature were abolished over the dorsal aspect of the feet and markedly impaired up to a level of about

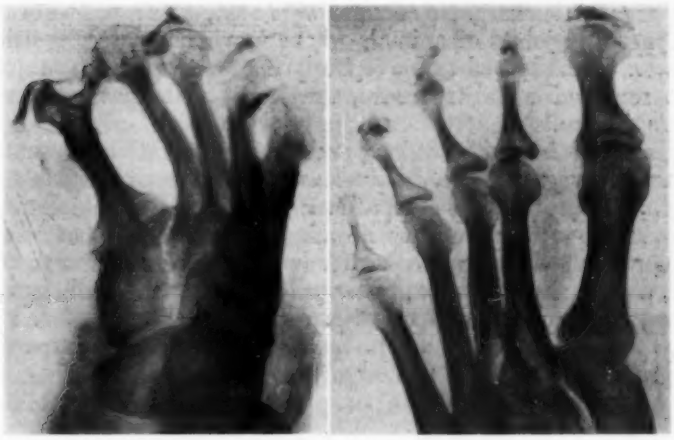


Fig. 8. Case 5. Bony changes characteristic of acro-osteolysis.

4 cm. above the malleoli. The sensory system of the upper limbs and the motor systems of the upper and lower limbs showed no abnormalities. Patellar and Achilles tendon reflexes: absent. Oscillometry reading: lower extremities normal. There was no difference in the readings taken before and after sympathetic block at the level of the eleventh thoracic dermatome. W. R. (blood and c. s. f.): negative. Microscopic examination of the spinal fluid showed no abnormalities. A smear of a scraping from the ulcer showed no acid-fast bacilli or fungi.

Roentgen findings (Fig. 8). The bony changes characteristic of acro-osteolysis (concentric bone atrophy) are clearly shown in the metatarsal bones of both feet and in the phalanges of the left foot (the phalanges of the right foot are completely destroyed). The shafts of the bones are slender and thinned out but the epiphyseal ends are mostly of normal appearance. The metatarso-phalangeal joints of the left foot are perfectly regular. Changes, due to chronic osteomyelitis, involve the first and the fifth metatarsal bones of the right foot.

The lumbar spine is markedly scoliotic and the vertebrae rotated. The bodies of L 4 and L 5 are asymmetric and slightly wedged to the left; there is a spina bifida of L 5.

Comment. The trophic influence of the nervous system on the bones has been a subject of discussion since the controversy between CHARCOT and VOLKMANN on the pathogenesis of tabetic osteo-arthropathies. This controversy gave rise to a considerable amount of research yielding contradictory results until the question was re-examined by ELOESSER and later by CORBIN under proper experimental conditions. ELOESSER (7) was able to demonstrate that section of the posterior nerve roots controlling a particular extremity did not in itself produce bone atrophy or a »Charcot's joint». In 1939, CORBIN and HINSEY (6) cut the nerve roots from L 4 to S 3 in cats and completed the denervation by removing the

lateral sympathetic chain. No changes were seen, over a period of 3 years, in the bones and joints of animals whose movements were restricted in small cages. Cats, allowed to move freely in large cages and subjected to constant repeated micro-traumata, developed arthropathies similar to »Charcot's joints».

CORBIN's work is significant in as much as besides ruling out any trophic influence of the central nervous system it excludes any possible similar effect from, or through, the sympathetic ganglia. On this latter point the clinical evidence is in agreement with the experimental data, as no atrophy or articular changes are met with after lumbar sympathectomy. There is, however, a profound difference between the osteoarthritic changes which accompany intraspinal lesions of the sensory pathways, *i. e.* in tabes dorsalis, syringomyelia and are occasionally met with in tumors, funicular degeneration, etc., and the osteolytic changes characteristic of both familial and sporadic acro-osteolysis.

Apart from the distribution of the skeletal changes which varies according to the level of the spinal lesion, the following characteristics are common to the osteoarthritic changes in tabes dorsalis, syringomyelia or any other lesion of the sensory system of the spinal tract.

1) The large, proximal joints (hip and knee in tabes, shoulder and elbow in syringomyelia) are predominantly affected.

2) The articular portions of the bones involved show a mixed destructive and reactive process (osteoporosis, coarse roughening of the articular surfaces, bone reaction and condensation with osteophytic proliferation).

On the other hand: the bone changes occurring in both familial and non-familial acro-osteolysis may be summarized as follows:

1) Progressive destruction of the distal bones of the feet without joint involvement.

2) The changes are exclusively of the osteolytic type and there are no signs of reaction in the remaining bones.

Such a fundamental difference between the two groups of osteopathies is possibly related to the different levels at which the sensory pathways are damaged or destroyed. While in the first group (tabes, syringomyelia, etc.) the nervous lesion is central to the posterior foot ganglia, in the second group (acro-osteolysis) there are good reasons to believe that the lesion of the sensory paths probably involves the peripheral fibres. The following points are in my opinion suggestive of the peripheral nature of the lesion:

a) The osseous lesions are most marked at the distal ends of the feet and gradually decrease proximally.

b) The sensory disturbances have a peripheral distribution (sock or stocking-like anesthesia) and never extend higher than the knees.

c) The type and distribution of the osseous lesions in acro-osteolysis bear a close resemblance to the changes characteristic of neural leprosy, in which the bone lesions are essentially of the osteolytic type and are maximal at the distal parts of the extremities. In leprosy, we find (1) the same concentric atrophy of the shafts of the phalangeal and metatarsal bones while the joints are unaffected. Furthermore, chronic ulcers and progressive mutilation of the extremities complete a picture that is very similar to acro-osteolysis. As a matter of fact acro-osteolysis has been mistaken for neural leprosy in more than one instance.

d) Finally, the normal appearances of the spinal cord at the autopsy of our case suggest that the lesion in the sensory paths may have been located in the peripheral fibres. (A post-mortem examination of a case of familial acro-osteolysis reported by LESSMANN (12) also revealed no changes in the spinal cord.)

The above arguments apply to both familial and non-familial acro-osteolysis. The fact that the sporadic type of acro-osteolysis is associated with malformations of the spine and possibly of the spinal cord, does not necessarily imply that they are causal agents. One might argue that the cause responsible for dysplasia of the spine and cord may interfere with a normal development of the terminations of the peripheral sensory nervous system in the extremities.

The etio-pathogenesis of the peripheral nerve lesion remains however obscure. Its similarity, mentioned above, to that occurring in neural leprosy leads one to suppose that it may be of an ascending although probably not of a chronic inflammatory type. It has been argued (10) that the so-called »neurotrophic osseous changes» are in effect the result of chronic osteomyelitis due to infection from the trophic ulcers. This view also finds support in certain research (17) in which it was demonstrated that after section of the sciatic nerve in cats, bony changes took place only in cases in which ulcers had developed. In my opinion, however, the type of osseous change (concentric atrophy), the absence of bone reaction, the fact that osteolysis is most evident in the terminal phalanges while the ulcers usually correspond to the extremities of the first and second metatarsals, are all arguments against a simple process of chronic osteomyelitis. But taken for granted that an organic lesion or a functional disturbance of the peripheral sensory fibres is the direct cause of acro-osteolysis, the mechanism of such a process remains unexplained; there is indeed no experimental evidence of any actual neurotrophic effect on the bones. For this reason, we prefer to designate acro-osteolysis as »neurogenic» rather than »neurotrophic». Even if the patho-

genesis of the »Charcot's joint» be understood, our present knowledge of the finer nervous regulation of the sensory, sympathetic and vaso-motory reflexes of the skeletal system does not appear to solve the problem of the pathogenetic mechanism of acro-osteolysis.

SUMMARY

Four cases of familial acro-osteolysis and one case of the sporadic type are reported.

Contrary to the prevailing opinion that acro-osteolysis is due to a pathologic condition of the spinal cord, the roentgen characteristics of the osseous changes and the neurological signs were suggestive of a lesion involving the peripheral sensory nerves.

ZUSAMMENFASSUNG

4 Fälle der familiären Akroosteolyse und 1 Fall des sporadischen Typus werden geschildert.

Im Gegensatz zu der vorherrschenden Meinung, dass die Akroosteolyse auf einem pathologischen Zustand der Wirbelsäule beruht, sprachen die röntgenologischen Charakteristika der ossösen Veränderungen sowie die neurologischen Symptome für eine Läsion der peripheren sensorischen Nerven.

RÉSUMÉ

Présentation de 4 cas d'acro-ostéolyse familiale et d'un cas d'a. o. sporadique.

Contrairement à l'opinion la plus commune, selon laquelle l'acro-ostéolyse est due à une affection médullaire, les caractères radiologiques des lésions osseuses et les signes neurologiques faisaient penser à une affection touchant les nerfs sensitifs périphériques.

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FROM THE DEPARTMENT OF RADIOLOGY (DIRECTOR: RAGNAR STEINERT),
AKERSHUS FYLKESSYKEHUS, OSLO, NORWAY

EFFECT OF ENEMATA ON CONTRAST EXCRETION IN UROGRAPHY

by

Ragnar Steinert

Correct evaluation of roentgenograms in urography requires careful preparation of the large bowel. It is the routine practice in Norwegian roentgen departments to administer castor oil two days before the examination followed by a two-litre enema immediately beforehand; the fecal matter which so often masks the outlines of the kidneys and the filled renal pelves and calices, obscures minor calculi and hides pathologic changes in the bladder, is thus largely removed.

This method of preparation does not appear to be a standard one throughout the world. It seems that in certain roentgen departments the administration of an enema on the day of urography is held to be contra-indicated in the belief that it may be retained, resorbed and being excreted through the kidneys, produce dilution of the contrast medium. It may be that attempts are made to overcome the insufficient preparation of the patient by varying and increasing the number of radiographic projections; eventually the examination may have to be repeated.

As it appeared difficult to obtain any exact information on the subject from the literature, the author carried out a few investigations on the influence of enemata upon urographic contrast density.

Fifteen patients were subjected to urography after being kept some twelve hours without fluids. Castor oil was administered two days beforehand supplemented by a 2-litre enema on the day of the examination. The evacuated enema was measured after filtration through gauze. Half an hour later a further 2-litre enema was administered; after evacuation, it was also collected and measured. Urography was then carried out. It was hoped by this form of preparation to secure the retention of an amount of fluid larger than after a single enema. An interval of half an hour was

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Fig. 1. Retention of 1,000 ml fluid after two enemata. Good contrast filling after fifteen minutes compression. (Injection of the contrast medium half an hour after evacuation of the last enema.)

allowed to lapse between the two enemata in order that as much as possible of the fluid of the first enema might be resorbed. A total of three quarters to one hour elapsed before both enemata had been passed and the patient was ready for urography.

In the 15 patients the total retention of both enemata ranged from 425 to 1,550 ml, of which 200 to 650 ml were accounted for by the first enema. Subsequent controls in a number of cases receiving single enemata have produced retention values between 100 and 600 ml (in one individual case 1,050 ml).

Among the 15 patients the contrast was satisfactorily concentrated in both renal pelves in 14 cases. Of a further 7 cases prepared with one enema, 3 were unsuccessful. Thus of a total of 22 examinations, 4 were unsuccessful. Three patients who retained 1,000, 1,500 and 1,400 ml respectively showed good contrast filling. In 3 of the unsuccessful cases the contrast was satisfactory on one side but unsatisfactory on the other. That the unsatisfactory filling occurred only on one side may be against the supposition that the clysmal fluid was the cause. In the fourth of the unsuccessful cases the excretion was poor on both sides; the examination was repeated later, the enema being withheld, but with the same result. It would appear therefore, that the unsuccessful result of the first examination in this case was not caused by the enema. Thus, in the total material of 22 cases there is no definite evidence that the enema had an adverse influence in any case.

It may seem surprising that urography is successful in spite of the retention of large amounts of fluid. The reason for this is probably due

to the roentgen examination being carried out before the enema fluid has been resorbed to any appreciable extent; hardly more than half an hour elapsed between the administration of the enema and the injection of the contrast medium. It is probable that the resorption of the enema fluid occurs slowly.

Certain patients who retained at least 350 ml of fluid after a single enema, were examined erect from half to one and a half hours later. Obvious fluid levels were seen in the large bowel in all these cases. The poor experiences with enema prior to urography in other countries may perhaps be due to the time from the enema until the contrast injection being too long — perhaps an hour or more. During this period the enema fluid may be resorbed and the contrast diluted.

The results obtained in these few cases may justify the following conclusions. In urography adequate preparation of the large bowel ensures such diagnostic advantages as well as possible economies in film consumption that the preliminary administration of enemata would appear to be essential. If the urography be carried out within half an hour — or at the most an hour — after the evacuation of the enema, the latter will generally have no obvious influence on the concentration of the contrast medium.

SUMMARY

Enemata prior to urography are usually considered to dilute the contrast medium. Careful preparation of the large bowel is, however, of considerable assistance in this type of investigation and the author shows that an enema of 2,000 ml has no apparent effect on contrast density providing the patient be examined within an hour of its administration.

ZUSAMMENFASSUNG

Man nimmt allgemein an, dass ein Einlauf vor einer Urographie das Kontrastmittel verdünnt. Sorgfältige Vorbereitung des Dickdarmes ist jedoch bei dieser Untersuchungsform von bedeutendem Nutzen und der Verf. zeigt, dass ein Einlauf von 2,000 ml keinen sichtbaren Effekt auf die Kontrastdichte hat. Voraussetzung ist dabei, dass der Patient innerhalb einer Stunde nach der Administrierung des Einlaufes untersucht wird.

RÉSUMÉ

On considère habituellement que les lavements précédant une urographie diluent le produit de contraste. Une préparation soigneuse du gros intestin facilite pourtant considérablement cet examen; l'auteur montre qu'un lavement de deux litres n'a pas d'effet appréciable sur la densité du contraste, à condition que le malade soit examiné dans l'heure qui suit l'administration.

FROM THE GYNECOLOGICAL CLINIC (DIRECTOR: PROFESSOR P. WETTERDAL) OF THE CAROLINE INSTITUTE, SABBATSBERG HOSPITAL AND THE DEPARTMENT OF RADIOPHYSICS (DIRECTOR: PROFESSOR R. SIEVERT), CAROLINE HOSPITAL, STOCKHOLM, SWEDEN

A STUDY OF THE SHORT-TIME EFFECTS ON THE MOUSE OVARY OF INTERNAL IRRADIATION WITH P^{32}

by

Erik Odeblad

Radioactive phosphorus is widely used in experimental investigations and in clinical work. The possible risk of irradiation damage to the gonads is then often a question of importance. The purpose of the present work is to present some contribution to the matter in the form of a study of certain short-time effects of internal beta irradiation with P^{32} on the ovary in mice.

Earlier Investigations

In 1948, BLOOM reported histologic ovarian damage in mice following the injection of 2.5 microcurie per g of body weight (μC/g) of P^{32}, 11 and 46 days after administration.

WARREN, MC MILLAN and DIXON (1950) studied the effects of internal irradiation in mice with P^{32}. The lowest dose reported originated from 25 μC per mouse, the animals being sacrificed 10 days after the injection. The follicles were affected and showed changes resembling normal atresia. These began in the inner granulosa layers, eventually affecting all the granulosa cells. Absence of the corpora lutea, condensation of stroma and late development of interstitial tissue was recorded. On the whole, a reduction of the total amount of ovarian tissue occurred.

Genetic changes following irradiation from P^{32} have been reported by BLUMEL (1950) and BATEMAN and SINCLAIR (1950).

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Experimental

54 female mature virgin mice, the stock inbred for more than twenty generations, were used. They all appeared healthy without signs of caloric, vitamin or mineral deficiency. The food consisted of corns and milk ad libitum. The animals (Strain An 51) were weighed and vaginal smears were taken daily.

The animals were divided in seven groups with eight animals in each. Group A received 0.1 μC/g of P^{32}, group B 0.3 μC/g, group C 1.0 μC/g, group D 3 μC/g, group E 10 μC/g and group F 30 μC/g. The radioactive phosphorus was given as orthophosphate in 0.2 ml of a carrier solution (containing 1.0 g Na_2HPO_4 per l of distilled water). Group K received 0.2 ml of the carrier solution without radiophosphate. The injection was performed subcutaneously. The cannula was inserted at the mid-point of the dorsum and was passed subcutaneously about 1.5 cm cranially. The deposit was made immediately behind the head in order to avoid direct irradiation of the ovaries. Immediately after injection, the solution introduced was squeezed up towards the head in order to prevent any backward leakage through the site of the puncture.

Four animals of each group were killed with ether 48 hours after injection and the remaining four 96 hours after injection. Immediately after death the abdomen was opened and the ovaries and the uteri were rapidly examined in situ. The ovary, together with the tube and the proximal part of the uterus, was placed in a fixing solution consisting of 6 per cent formalin and 0.5 per cent trichloracetic acid in distilled water. Fixation was allowed to start at + 4° C in order to prevent postmortal changes in the tissues, and for the same reason no time was occupied in obtaining weight data. The specimen was then embedded in paraffin in the usual way and cut into sections, 4 or 10 μ thick, which were mounted on methacrylate slides and deparaffinized in xylene and ethanol. Contact autoradiography, using Gevaert Dentus Rapid Roentgen film, was then carried out. After exposure (3—30 days) the films were developed in Kodak DK 20 developer with an additional 0.2 per cent potassium bromide. The reverse side silver was removed with Farmer's solution. The sections were stained according to MALLORY (1936) or with haem-alum-eosin.

Results

1. General condition of animals.

One day after the injection all animals in groups A—E and group K appeared normal. In the animals in group F, an ulcer, 3 × 4 mm in size, had occurred at the site of deposit of P^{32}. Two days after injection, small

ulcers were also visible in 3 out of 8 animals in group E. In group F the ulcers were covered with a fibrinous layer, and these animals appeared to be less lively than the others. Similar conditions prevailed after three and four days.

The body weight showed the course illustrated in fig. 1. A considerable decrease appeared in group F.

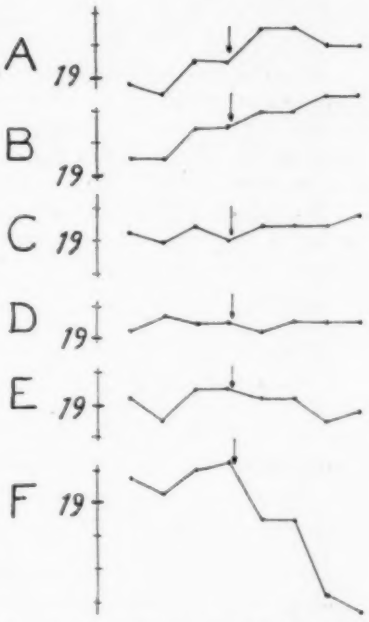


Fig. 1. Mean weight curves for various groups. The subdivisions on the ordinates indicate grams. Each point represents the mean weight for one day. Injection of P^{32} indicated by arrows.

2. The vaginal smears.

The examination of vaginal smears in mice can usually give an indication of ovarian function. Radiation-induced changes in the vaginal smears (GRAHAM, 1951) may however complicate the issue.

Before the injection of P^{32}, all the animals were found to have regular vaginal cycles. After the injection cyclic changes persisted except in groups E and F in which squamous epithelial cells were not found; this may indicate impaired ovarian function.

3. Appearance of the internal genital organs in situ.

After two days no definite changes were found. The ovaries contained haemorrhages and the uteri were of normal appearance in all the groups of animals. After four days, there were normal conditions in groups A—C and group K. In groups D—F the uteri and the ovaries were small and pale. No signs of recent haemorrhages were seen, indicating inhibition of ovulation.

4. Microscopic findings on the internal genital organs.

Ovary. The histologic changes, visible in the ovaries were most pronounced in the follicular granulosal tissue (tab. I, figs. 2 and 3) and less pronounced in the theca interna and young corpora lutea. The interstitial gland appeared, from the morphologic point of view, to be the least radiosensitive.

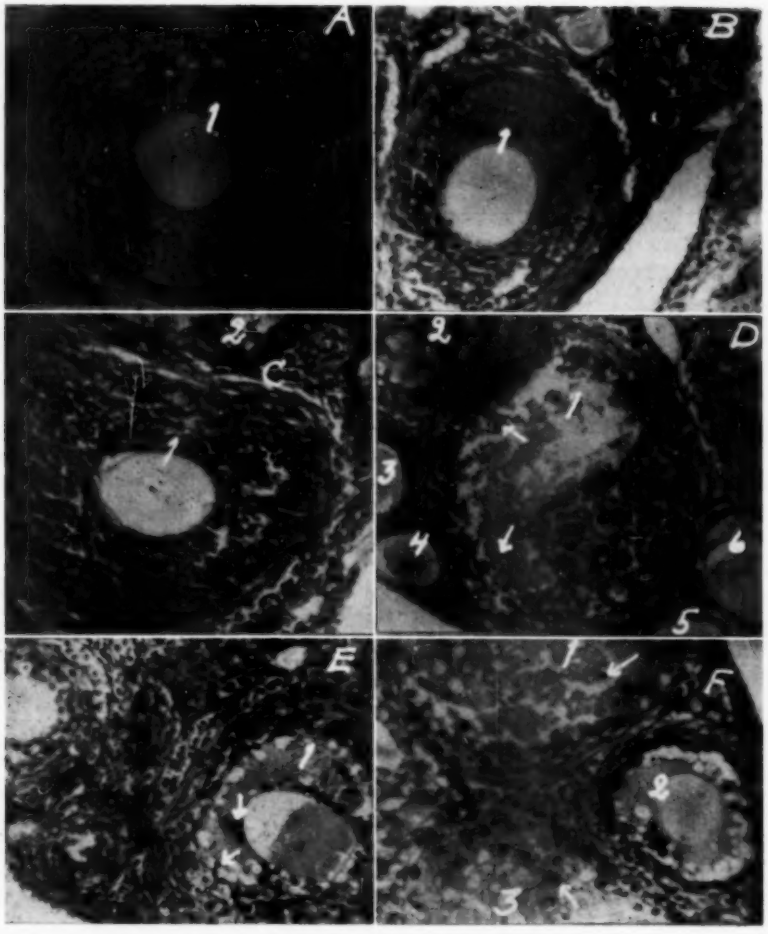


Fig. 2. Typical follicles of comparable sizes in the groups A—F 96 hours after injection of P^{32}. × 180.

A. The follicle is shown at 1 and presents a quite normal appearance.

B. The follicle at 1 has an apparently normal structure.

C. Fissures are present in the granulosal tissue. It is difficult to decide whether these are due to histologic artefacts or to slight irradiation damage.

D. In follicle 1 (the ovum outside the section) changes have occurred in the inner granulosal cell layers with slight reduction of the thickness of the granulosal tissue. In the smaller follicles 3—6 damage of the granulosa could also be recorded. Arrows indicate nuclear fragments.

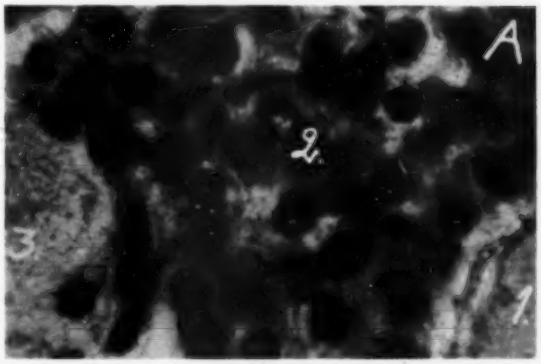
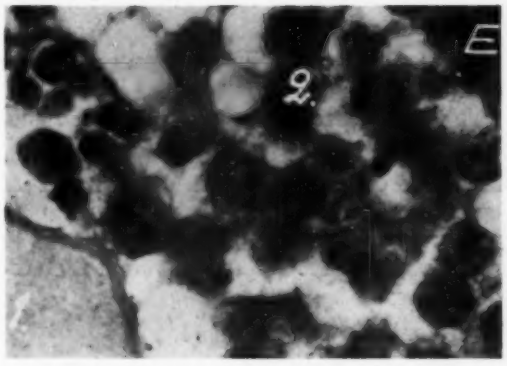


Fig. 3 A and E. Details of granulosal tissue from group A and group E. × 1300.

A. Regularly formed nuclei (2) and a part of the ovum (1) are visible, both morphologically normal.



E. The cytoplasm of the ovum (1) appears normal. A large number of vacuoles replace former granulosal cells (2). Abundant nuclear fragments and pycnotic and irregularly formed nuclei present.

In the follicles reduction of the thickness of the granulosal layer, at first affecting the inner layers of cells had occurred. On high magnification bizarre cellular and nuclear forms were visible. Swelling and vacuolization occurred in the cytoplasm and pycnosis and nuclear fragmentation were noted in the cell nuclei. The border between the granulosa and the theca had become indistinct.

In the corpora lutea and the interstitial gland slightly irregular cellular and nuclear forms were seen.

E. In follicle 1 severe changes with pronounced reduction of the granulosa layer, vacuolization and presence of nuclear fragments (arrows). In follicle 2 the changes are less pronounced although clearly visible by eye in the microscope.

F. Intense destruction of follicles 1—3. Nearly all the visible granulosal cells show serious damage. Nuclear fragments (arrows) and vacuoles, apparently replacing former granulosal cells are visible. The surrounding parts of the interstitial tissue also present irregular cell and nuclear signs.

Table I

Histologic damage of the granulosal tissue in various groups

Group	48 hours	96 hours
A	0	0
B	0	0
C	0	0
D	(+)	+
E	++	++
F	++	+++
K	0	0

0 = no damage
(+) = hardly visible damage
\+ = slight damage
++ = moderate damage
+++ = extreme damage

The changes in the granulosa cells occurred with certainty in group D and at higher dosage, while the changes in the theca, the corpus luteum and the interstitial gland were not indefinite below group F.

Uterus. The picture of the endometrium can often be taken as an index of ovarian function. However, radiation-induced changes in the endometrium may occur as a highly complicating factor. In group F signs of evident estrogenic stimulation of the endometrium were probably lacking, though it is questionable if such a conclusion be justified.

5. Autoradiographic changes.

The autoradiographic density depends on the thickness of the section, the histologic geometry during the exposure and the duration of the latter as thoroughly described elsewhere (ODEBLAD, 1952). The histologic changes due to radiation damage make a quantitative comparison of the autoradiographs difficult. The following two findings may, however, be regarded as constant.

Firstly the principal features of autoradiographic films of ovaries (ODEBLAD, 1951) appear to persist throughout the whole series A—F. These principal features are: A moderate uptake of P^{32} in the interstitial gland, a considerable uptake in normal follicles (except very young normal follicles), a small uptake in atretic and very young normal follicles, and again a considerable uptake in the corpora lutea.

Secondly, there appears to be relatively reduced amounts of P^{32} in the sections after the higher doses. This suppression of density seems to affect especially the Graafian follicles.

Discussion

The histologic changes recorded are chiefly of the same nature as those described by WARREN, MC MILLAN and DIXON (1950) and BLOOM (1948). The changes in the granulosal tissue observed in this study were found to be most striking, while the corpus luteum and the interstitial gland appear less radiosensitive.

The suppression of autoradiographic density, found at the higher doses is, with due regard to the findings of HEVESY and coworkers (1948) and HOLMES (1947, 1949), interesting and indicate decreased renewal of nucleic acids, following subjection to ionizing radiation. As both direct and indirect effects were found by these authors, one must bear in mind that the changes now recorded may be due partly to direct irradiation of the ovary and partly to indirect intoxication from the remainder of the body, which is also irradiated.

It is worthy of note that the changes following internal irradiation by P^{32} produce appearances in the granulosal tissue, similar to those found in spontaneous atresia, recently summarized by BLOCK (1951). In this respect such changes may reflect a type of reaction of the granulosal tissue when undergoing degeneration from various primary causes.

SUMMARY

Adult female mice were given 0.1, 0.3, 1.0, 3, 10 and 30 μC of P^{32} per g and killed after 48 or 96 hours. At the higher doses there was a considerable loss in weight and signs of estrogenic stimulation were absent in the vaginal smears and the endometrium; autoradiographs showed a decreased uptake of P^{32}. In the ovary the granulosa tissue was most radiosensitive, changes appearing at 3 μC/g. The interstitial gland appeared to be the least radiosensitive, the other tissue components having intermediate sensitivities.

ZUSAMMENFASSUNG

Ausgewachsenen weiblichen Mäusen wurden Dosen von 0.1, 0.3, 1.0, 10 und 30 μC P^{3} per g gegeben und dann nach 48 oder 96 Stunden getötet. Nach den höheren Dosen trat ein bedeutender Gewichtsverlust auf und Zeichen östrogener Stimulierung waren in Vaginalausstrichen und im Endometrium nicht vorhanden; Autoradiographien zeigten eine herabgesetzte Aufnahme von P^{32}. Im Ovarium war das Granulosazellgewebe am strahlenempfindlichsten; Veränderungen traten zuerst bei 3 μC/g auf. Die interstitielle Drüse schien am wenigsten strahlenempfindlich zu sein; die übrigen Gewebskomponenten hatten eine zwischen diesen beiden liegende Radiosensibilität.

RÉSUMÉ

Des souris femelles adultes reçurent 0.1, 0.3, 1.0, 10 et 30 μC de P^{32} par gramme et furent tuées au bout de 48 ou 96 heures. Les souris soumises aux doses les plus élevées avaient subi une perte de poids considérable et leur endomètre et leurs frottis vaginaux

ne présentaient pas de signes de stimulation oestrogénique. Les autoradiographies montrèrent une fixation diminuée de P^{32}. Dans l'ovaire, la granulosa est le tissu le plus radiosensible, des lésions apparaissent pour 3 μC./g., la glande interstitielle est le moins radiosensible; les autres tissus ont des sensibilités intermédiaires.

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FROM MOUNT VERNON HOSPITAL AND THE RADIUM INSTITUTE, NORTHWOOD, MIDDLESEX, ENGLAND

A FLEXIBLE LINEAR GAMMA-RAY SOURCE (Co^{60}) FOR THE TREATMENT OF CANCER OF THE UTERINE BODY

by

D. E. A. Jones

Introduction

The method most widely adopted for the gamma-ray treatment of cancer of the uterine body involves the insertion of a single linear radium source into the uterine canal. Such a source often consists of an end-to-end arrangement of equal radium tubes, the number used depending on the length of the uterine cavity.

From the viewpoint of physical dosage distribution, this method leaves room for improvement since the isodose configuration does not conform to the contour of the uterus. The discrepancy is particularly marked at the fundus, a very common site of origin of carcinoma and of its later recurrence. Some improvement of dosage distribution is of course possible, if the radium tube at the distal end of the applicator has a higher content than the other sources, but the end-screenage effect of such an arrangement still results in a relatively low dose in the axial direction.

The well-known »packing» technique developed in recent years at the Radiumhemmet, Stockholm (HEYMAN et al., 1941), is a noteworthy attempt to improve the dosage distribution, particularly for uterine cavities which are wide or irregular, or both. By filling the cavity with a large number of relatively small separate radium units, a favourable physical distribution of dose has been obtained irrespective of the size and shape of the cavity.

This method unfortunately involves a multiplicity of special apparatus and of radiators, ten to twenty of which are used at each application

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and are inserted separately. The authors admit that a certain amount of experience, and great caution, is required in packing the uterus and that perforation is unavoidable in a number of cases.

We therefore sought to achieve the desired dosage distribution by a simpler and safer form of applicator. The desired criteria were that the apparatus should consist of a single radiator capable of delivering a dose of at least 6,000 *r* to all significant parts of the uterus, whatever its size and shape, in two equal periods of about 24 hours, separated by one week.

A line of attack which seemed both feasible and promising was to introduce into the uterine cavity through the cervical canal, a linear gamma-ray source in the form of a very flexible loop which, after passing the internal os, would expand so as to press against the lateral walls and the fundus of the uterine cavity. A close helix of 0.5 mm diam. stainless steel wire was made up to a diameter of about 4 mm in a 15 cm length. Using post-mortem uteri, it was found that this helix could be passed easily as a narrow loop through a thin-walled metal tube of 1 cm diameter which was inserted into the cervical canal after dilatation. Its springy nature then enabled the loop to expand into the cavity in the desired manner.

To convert such a loop into a linear gamma-ray source, and maintain at the same time the desired mechanical flexibility, involved using very short individual sources. For reasons referred to in a later section, it was decided to use short rods of radioactive cobalt (Co 60) rather than radium tubes.

Description of Apparatus (Fig. 1)

A length of 24 gauge (0.56 mm diam.) stainless steel wire is wound into a close helix (A) of the required length (usually about 15 cm) and of 3.75 mm outside diameter. Its ends are then pushed into corresponding holes in a brass cylinder B, 2 cm long and 1.95 cm diam., drilled on either side of the long axis of the cylinder. The loop thus formed acts as a flexible container for the gamma-ray sources. This container is closed by means of a brass plug C having two stainless steel plugs which fit corresponding holes drilled in the end of the brass cylinder remote from the loop. When the loop is compressed laterally it may be passed through the »cervix tube» D. This is a short thinwalled brass tube of 1 cm outside diameter with a 2 cm diameter flange at one end. The flange is slotted across a diameter to receive a corresponding brass key on the plug which, when engaged with the slot, lies at right angles to the plane of the flexible loop.

The simple method described above for attaching the ends of the loop to the brass cylinder is such that it requires a considerable pull on the loop to detach it from the cylinder provided the ends of the loop enter the holes to a depth of at least 5 mm. This depth of insertion provides an easy means of adjusting the loop to the required length.

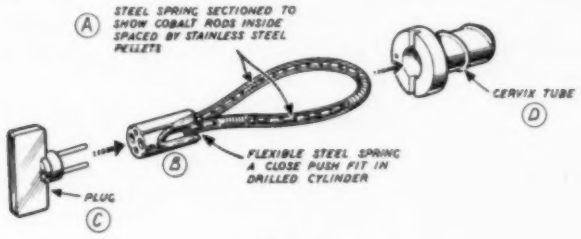

Fig. 1.

A short piece of copper wire is soldered to the outer cylindrical surface of the cervix tube to form a quick right-handed screw thread, making about 1 ½ turns over the 2 cm length of the tube.

Assembly and Insertion of the Applicator

At a preliminary examination under anaesthesia the distance between external os and fundus is determined by means of a graduated uterine sound. An appropriate length of helical stainless steel is then selected and mounted in the brass cylinder so that the required length of loop is obtained. This is then loaded with the appropriate number and arrangement of Co^{60} rods and spacers (to be described later) so that the tunnel formed by the loop and the attached cylinder is completely filled up. The applicator is closed by means of the plug and secured with a silk thread passed through suitable holes drilled in cylinder and plug. It is then sterilised together with the other parts of the apparatus.

With the patient in the lithotomy position, the cervix is progressively dilated, normally up to about a Number 8 Hegar. (Cervix tubes of larger external diameters are available for unusually patulous os.) A cranked introducer supporting the cervix tube is inserted into the cervical canal and then withdrawn to leave the tube in the cervix. A clockwise rotation of the tube through one or two turns, aided by the screw thread, ensures that the tube is gripped reasonably firmly by the cervix. The slot in the flange of the cervix tube should be parallel to the vaginal axis.

The loaded applicator is gripped in special forceps close to the end of the loop so that the two sides of the loop are brought into contact.

The tip of the loop, thus narrowed, can then be inserted into the cervix tube. The applicator is then pushed forward and upward until the brass cylinder is fully inserted in the cervix tube and the key on the plug is engaged with the slot. It is held in this position while the vagina is packed in the usual way.

The applicator is removed without difficulty by the house surgeon in the ward at the specified time. No anaesthetic is required. The silk threads attached to both cervix tube and plug facilitate this process.

Dosage Distribution

The applicator was planned to fulfil as far as possible the following dosage criteria, within the limits imposed by the desired functional and constructional simplicity:

(a) The delivery of at least 6,000 *r* in two 22-hour periods to a closed surface at a uniform distance of 1 cm from the piriform plane, representing the transverse section of the uterine cavity, as outlined by the inserted loop of the applicator and the cervix tube.

(b) The limitation of the maximum dose received by the uterine body to a value which, under the proposed treatment conditions, would not involve a serious risk of necrosis.

As regards (b), the form of the applicator necessarily implies maximal dosage very locally along the line of contact between the spring and the endometrial surface. Tod (1948) gives »over 30,000 *r*« as the tolerance level for the wall of the uterus on the basis of 8 days' continuous irradiation by radium techniques. Calculation indicated that to satisfy condition (a) at the fundus with the loop applicator, the maximum surface dose in this region might approach 50,000 *r*. This high dose region would, however, be localised to superficial tissues actually in contact with the spring.

Preliminary dosage measurements were made, using a small (air volume 0.2 cc) graphite ionisation chamber, with the applicator loaded with short 5 mg radium tubes. (30 × 5 mg radium tubes, length 6 mm, active 4 mm, diam. 2.25 mm, were kindly loaned to us by Dr. T. M. Robb, Director of the Radiotherapy Department at Lambeth Hospital, London.) Calculations based on the dosage distribution thus obtained, indicated that the desired criteria could reasonably be satisfied if the applicator were loaded with a linear distribution of radioactive material equivalent to 6.0 mg per cm of radium (in 0.5 mm Pt) except at the tip of the loop. Here a loading of about twice this intensity (12.6 mg per cm) would be necessary to ensure the desired depth dose at the fundus.

The length of the individual radium tubes was found to impede the easy passage of the loop through the cervix tube, and trials with dummy rods inside the spring container showed that the desired mechanical flexibility could only be ensured if the rods did not exceed 4 mm in length. Such short radium tubes, with their necessarily high ratio of inactive to active length, might be expected to increase the already high local dose to the immediately adjacent tissues. For this reason it was decided to use radioactive cobalt (Co 60) sources. This isotope was readily available from Harwell in the required size and specific activity.

It was decided to use cobalt wire 2 mm in diameter in lengths of 3.4 mm, electroplated all over to a thickness of 0.1 mm of nickel. It was hoped that this thickness of nickel, while adequate to absorb the 0.3 MeV β-rays (MAYNEORD, 1950), would also be effective in eliminating the toxic tissue reactions noted in animal experiments involving the interstitial use of bare Co 60 (NICKSON, LAMERTON and MAYNEORD, 1949). Further reference to this is made in a later section.

To give the desired maximum linear intensity, the individual sources needed to be about 2.8 mc each, a figure which would allow for the use of the same sources for a 12-month period, the radioactive decay being about 1 per cent per month. To simplify loading and to avoid the risk of confusion between small unmarked sources of different activity, it was decided to space the active units with 4 mm long stainless steel pellets where the lower linear activity was needed.

Thirty of these nickel-plated 2.8 mc units were prepared for us by the Isotope Division at Harwell. A full dosage survey in the two principal planes of the applicator was then made with the loop length adjusted to correspond to an 8 cm long uterine cavity. The total load was 74 mc. The tip of the loop contained 6 contiguous cobalt sources and the remainder of the applicator was filled with alternate sources and spacers, 20 of each, the loading being symmetrical about the long axis.

The isodose distributions in the two planes are shown in terms of r per hour in figure 2, where the dotted line shows the position of the closed surface as defined in (a) above. For this surface, a minimum dose of 6,000 r requires a treatment time of 43 hours, the corresponding maximum dose being 10,000 r, with the average probably nearer the lower value. The maximum doses at the applicator surface occur along a 2 cm line between points X at the tip of the loop and also very locally at Y, reaching the same value, about 45,000 r, in each case.

As would be expected from the »linear» form of the source, the dosage distribution relative to the surface of the applicator will be practically independent of the length of the loop, provided the linear intensities employed remain unchanged. This was verified experimentally during the earlier measurements with radium sources when a complete dosage

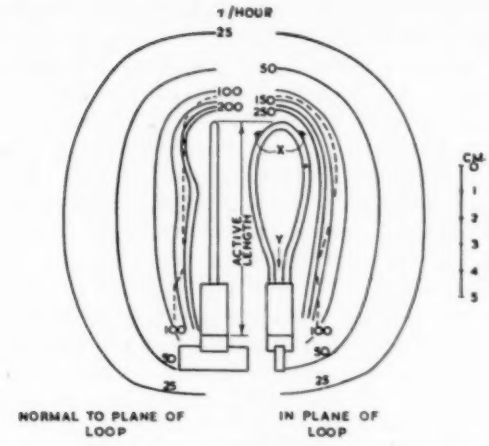

Fig. 2. Isodose distribution for 74 mc load (Co^{60})

survey of the applicator was made using two sizes of loop corresponding to a 5.75 and an 8 cm uterine cavity. This convenient finding enabled us to standardise the treatment time irrespective of the size of the cavity.

The sources will normally be returned to Harwell for reactivation every 12 months. By the end of this time the loss of activity corresponds to 12.3 % and the time for each of the two treatments reaches 24.5 hours.

Clinical Trials

The applicator has been used for the radical gamma-ray treatment of 5 cases of uterine body cancer over a period of twelve months. The present follow-up (maximum 16 months, minimum 5 months) shows all patients to be free of symptoms with no clinical evidence of recurrent or residual disease in the pelvis or elsewhere. There has been no evidence whatever of radionecrosis. Long-term follow-up results will be reported later. The results to date are, however, regarded as sufficiently promising to warrant the continued use of the method.

The Effectiveness of the Nickel Plating

The feasibility of using Co^{60} as an alternative to radium as a gamma-ray treatment source has been discussed elsewhere (*e. g.* MAYNEORD, 1950; MESCHAN et al., 1951; WILSON, 1951; WAKELY, 1951). There would appear to be ample justification on a physical basis for accepting the

biological equivalence between a gamma-ray dose measured in r from radium (0.5 mm Pt filter) and from Co^{60}.

As regards the nickel-plated coating, our measurements with a beta-ray ionisation chamber having a thin paper window (1.8 mg cm^{-2}) gave no evidence of beta-ray emission from the plated sources, while similar measurements on bare cobalt rods showed that a paper thickness corresponding to about 45 mg cm^{-2} was required to absorb the beta radiation. The plated nickel was about 0.1 mm thick ($\sim$ 89 mg cm^{-2}) and was clearly adequate in this respect.

As a toxicity barrier, however, the plating has not proved entirely satisfactory. Immediately following each treatment, the gauze plug for packing the vagina was found to be slightly radioactive. No activity has, however, been detected in the excreta nor has any patient shown residual radioactivity. A similar transfer of activity occurs when individual plated sources are immersed in plasma at body temperature.

Pending the outcome of further experimental work now in progress here (to be published in a later paper), and of a modified nickel-coating technique under investigation at Harwell, the original plated sources will continue to be used, under careful contamination control, for the treatment of suitable cases.

Acknowledgements

Dr. Paul Strickland, at whose request for an improved method for radical treatment of cancer of the uterine body the applicator was designed, has been responsible for the clinical side of the investigation and has given us most valuable advice. The patients were admitted for treatment under the care of Professor Windeyer and Dr. Roy Ward without whose encouragement the work could not have progressed. The bulk of the dosage measurements and the related graphical work were carried out by Mr. I. Birchall. The applicator and the associated apparatus was constructed by Mr. T. Marshall in the Physics Department workshop.

We are greatly indebted to the Isotope Division A. E. R. E., Harwell, for their collaboration in the preparation of the Co60 sources and also to Mr. Roy Cross, Aviation Journalist and Technical Artist, who prepared the »exploded« drawing Fig. 1 and presented it to the Hospital.

SUMMARY

A description is given of a simple form of applicator for the treatment of cancer of the uterine body, embodying a flexible linear gamma-ray source. This source, loaded differentially to give a favourable physical dosage distribution, particularly at the fundus, consists of a series of short rods of metallic Co^{60} supported within a closely wound helix of stainless steel wire. This forms a loop contained by the endometrial surfaces and is adjustable in length to fit the dimensions of the cavity. The individual sources are nickel-plated to absorb the 0.3 MeV beta rays and to obviate toxicity reactions.

ZUSAMMENFASSUNG

Es wird ein einfacher Applikator für die Behandlung des Karzinoma corporis uteri beschrieben; er enthält eine biegsame lineare Gammastrahlenquelle. Diese Quelle, die so aufgeladen ist, dass sie eine günstige physikalische Dosisverteilung, besonders für den Fundus, gibt, besteht aus einer Serie von kurzen Stangen metallischen Co^{60}; diese werden durch eine eng gewundene Spirale aus rostfreiem Stahl zusammengehalten. Diese bildet eine Schlinge, die durch die endometriale Oberfläche geformt wird und die in ihrer Längsausdehnung so beweglich ist, dass sie sich den Dimensionen der Kavität anpasst. Die einzelnen Strahler sind vernickelt, um die 0.3 MeV Betastrahlen zu absorbieren und toxische Reaktionen zu vermeiden.

RÉSUMÉ

Description d'un type simple d'applicateur pour le traitement du cancer du corps de l'utérus, comprenant une source linéaire et flexible de rayons gamma. Cette source est constituée par une série de courts fragments de fil de Co^{60} métallique, distribués non pas régulièrement mais de façon à donner une répartition convenable de la dose, en particulier au fond du corps utérin, et placés dans un ressort à spires jointives d'acier inoxydable. Ce ressort forme une boucle contenue par les surfaces endométriales, et est ajustable en longueur aux dimensions de la cavité. Les fragments de fil de Co^{60} sont recouverts de nickel pour absorber le rayonnement bêta de 0.3 MeV et pour empêcher les réactions toxiques.

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FROM THE RADIUM CENTRE (DIRECTOR: JENS NIELSEN) AND ASSOCIATED HISTO-PATHOLOGICAL LABORATORY (HEAD: F. BANG), COPENHAGEN, DENMARK

SOME CLINICAL AND HISTOLOGIC OBSERVATIONS ON »PRECANCEROSES» OF THE PORTIO VAGINALIS UTERI

With special reference to the frequency of the development of cancer

by

Olaf Petersen

The difficulties confronting the clinician and especially the histologist in assessing those changes in the mucosa of the portio vaginalis which have passed under the much debated designation 'precanceroses', have long been appreciated. A final solution of the problems is far from being achieved, either as regards the placing of this group in the classic distribution of malignant or benign or from the point of view of treatment.

In most cases the examination of a section removed at biopsy from a suspicious area of the portio vaginalis will establish the diagnosis of cancer or give a negative result; the investigator, however, must realize that this relatively rough method of investigation cannot be expected to afford a precise answer in all cases. The border-line between benign and malignant tissue changes is not well-defined, clinically or histologically; a series of processes must be presumed to constitute the links in the transformation into malignancy, and the various intermediate stages cannot all be expected to be reflected as morphologic changes visible in a microscope. Certain structural deviations from the normal have, however, been interpreted as definite indications of malignant changes and infiltration has up to the present been a *sine qua non* in the histologic diagnosis of cancer. Intensive cytologic studies carried out in recent years have aimed at finding criteria in the structure of the individual cell which would permit the question of malignancy to be decided without reference to other tissue cells.

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It would thus seem that invasion of tissue as an essential feature in the histologic diagnosis of cancer no longer obtains and that clinicians tend to accept this viewpoint; the sixth volume of the »Annual Report on the Results of Radiotherapy in Carcinoma of the Uterine Cervix» (published in 1951) has admitted intra-epithelial processes, described as carcinoma in situ, pre-invasive carcinoma or intra-epithelial carcinoma, as a sub-group of cervical carcinomas, with the stage designation 0. By far the great majority of investigators who have concerned themselves with the problem, are inclined to look upon certain changes in the mucosa as irreversible precursors of cancer, or simply as cancer. These changes may be characterized by cytologic deviations from the normal which although without invasive characteristics it may be difficult, or impossible, to discriminate from those occurring in atypical malignant neoplastic cells.

Therapeutically, this tendency has been manifest in that radical procedures in the form of total hysterectomy or radium treatment have been extensively carried out in such cases. This attitude has been especially predominant in the American literature (9, 19, 21, 23). Hoge (7) sent out questionnaires on the methods employed in the treatment of carcinoma in situ to 79 medical schools in the U. S. A. and Canada. The replies received from 77 showed that total hysterectomy or total hysterectomy with salpingo-oophorectomy was employed in such cases at 67 while only one hospital recommended repeated histologic or cytologic controls during a period of observation.

From various, highly competent sources (11, 12, 13, 14) warnings have been sounded against too active procedures. These, it will be realized, will be performed on women mainly in the reproductive age; the mean age of patients with changes in the portio mucosa, as far as can be gathered, is about one decade below the mean age of patients with manifest cancer of the uterine cervix (7, 16, 26). Even with the present improvements in anaesthetic and operative technic, the operative mortality in total hysterectomy can hardly be expected to be less than about 0.5—1 %; this figure cannot be ignored when, after all, we are concerned with changes the possible malignancy of which is uncertain, or at any rate unclarified.

Epithelial changes of the portio consisting of atypical cells without invading properties, may develop further and in a number of cases invasion of the subepithelial stroma may occur after a certain latent period. This may be accepted as having been established by most authors (1, 2, 5, 8, 10, 15, 17, 18, 20, 22), but a few reports exist of changes that have proved reversible and have regressed spontaneously (3, 25). Observation over long periods of time, occasionally over many years, will be required to reveal the true nature of these changes, but the predominantly radical

treatment has evidently been responsible for the very scanty reports in the literature of a spontaneous course of the so-called precanceroses.

Writer's Material

Since 1938 the Radium Centre in Copenhagen has not, in general, submitted patients with so-called pre-cancerous changes in the mucosa of the portio to radical treatment but confined itself to an attitude of watchful expectancy with repeated biopsies and examination of excochleations from the cervical canal. The material thus obtained, which forms the basis for this paper, has been selected in the sense that only patients in whom malignancy was suspected at their first examination have been referred to the Radium Centre. It therefore appears reasonable to assume that the material is made up of the most advanced cases while those with less pronounced atypical epithelium may easily have been under-represented. No general conclusions can therefore be drawn from the figures.

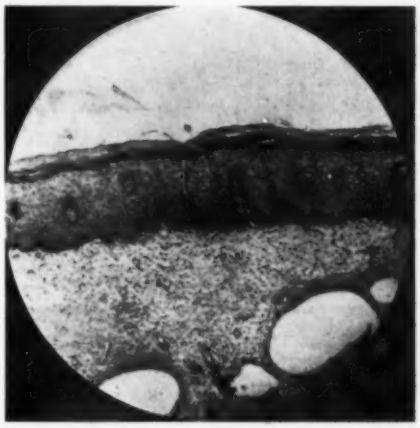
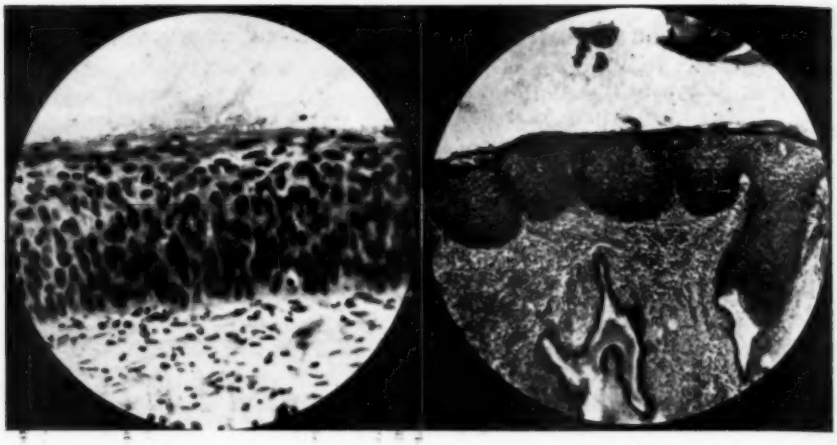


Fig. 1. Simple epithelial hyperplasia. The epithelium is thickened, but normal stratification is retained; no abnormal cell nuclei in evidence. × 60.

During the period 1938—45, 104 patients were referred for cervical lesions but not treated radically. In these cases sections removed from suspicious areas of the portio vaginalis did not reveal frank cancer but showed pre-cancerous proliferative processes of varying degree and anaplasia. I have divided them into the following three categories: 1) simple epithelial hyperplasia, 2) epithelial hyperplasia with nuclear abnormalities — non-invasive carcinoma, 3) borderline cases with doubtful frank invasion.

By *simple epithelial hyperplasia* is meant a simple thickening of the epithelium with retention of stratification, intact basement membrane and no nuclear abnormalities (fig. 1).

By *epithelial hyperplasia with nuclear abnormalities: non-invasive carcinoma* is understood a change in the epithelium towards anaplasia so that throughout the whole thickness of the epithelium, or a large part of it, nuclei, differing distinctly from the normal in size, form and stainability are in evidence; at the same time the stratification of the epithe-



a. b.

Fig. 2 a + 2 b. Epithelial hyperplasia with nuclear abnormalities: non-invasive carcinoma. The stratification of the epithelium is blurred. The cells nuclei are small and darker than normal. Many mitoses in evidence. The margins with the subepithelial connective tissue is well demarcated everywhere. In fig. 2 b down growth of epithelium into a gland is seen. 2 a: × 300. 2 b: × 60.

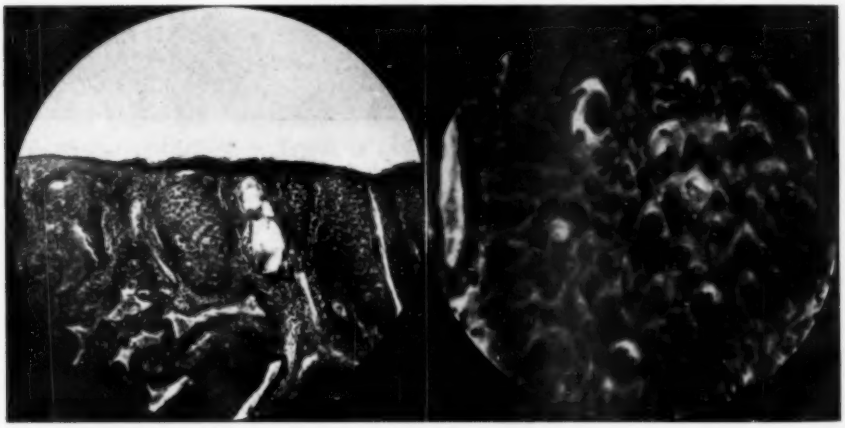


Fig. 3. Borderline cases with doubtful frank invasion. Atypical epithelium with cone-shaped and bulb-shaped elongations into the underlying round-cell infiltrated stroma. Downgrowth of squamous-cell epithelium into the glands; no definite invasive growth, however. × 60.

Fig. 4. Higher magnification of epithelium shown in fig. 3. Marked nuclear abnormalities. × 300.

lium is blurred. Moreover the number of mitoses is generally increased. There is occasionally involvement of the glands. (Fig. 2.)

Borderline cases with doubtful frank invasion refers to epithelium in which nuclear changes resembling those seen in »epithelial hyperplasia with nuclear abnormalities: non-invasive carcinoma» occur but, in addition, the examination of one or more sections suggests but reveals no definite evidence of infiltration. (Figs. 3, 4.)

As always when attempting to divide a biologic material into groups, the division naturally becomes arbitrary; this holds true particularly for the last-mentioned two groups, where the distinction is based solely on the pathologist's judgment. This may be said to apply to HINSELMANN's (4, 6) division of the same epithelial changes into 4 groups, each consisting of 3 subgroups. »Epithelial hyperplasia with nuclear abnormalities: non-invasive carcinoma» corresponds in some degree to Hinselmann's groups III and IV (or as it is designated in other works, pre-invasive carcinoma, intra-epithelial carcinoma, Bowen's disease of the cervix or, now officially, stage 0). Histologically, »borderline cases with doubtful frank invasion» occupies a position between these changes and frank infiltrating cancer.

The age distribution of the 104 patients who were not submitted to radical treatment, will be seen from Diagram 1. The summit of the curve

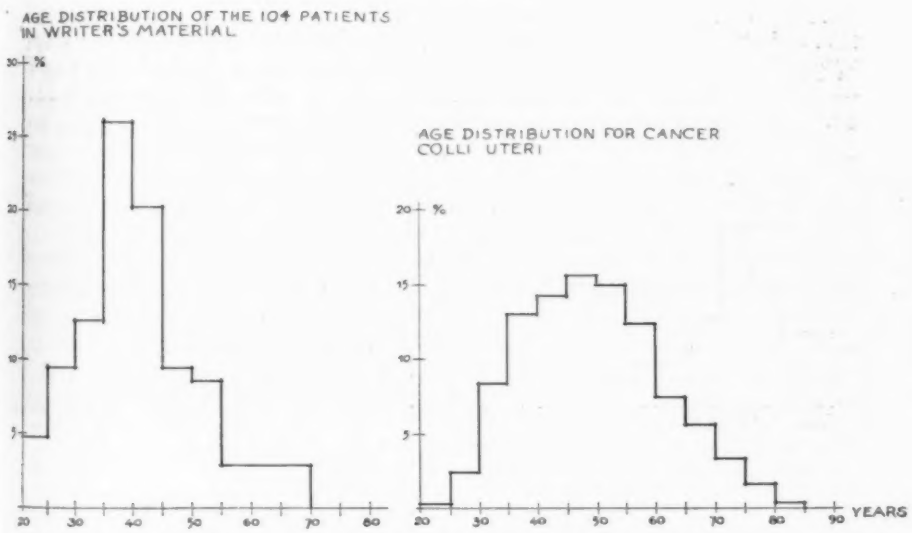


Diagram 1. Age distribution of 104 patients with atypical portio epithelium, compared to that of 2,918 patients with cancer of the uterine cervix (after TRUELSEN).

lies between 35 and 40 years. The mean age of the patients when first seen at the Radium Centre was 40.2 years. If a comparison be made with the age distribution curve of clinically manifest cancer of the uterine cervix, taken from TRUELSEN's work (24), it will be seen that the summit of that curve lies between 45 and 50 years. The difference in the ages may perhaps be taken as an indication of the latent period, *i. e.* the time elapsing before the precancerous changes merge into clinical cancer.

The mean age of the patients in the writer's material agrees fairly well with the mean age of 40.8 years reported by PUND et al. (15) in 63 patients with so-called »pre-invasive cancer», of 37.7 years by YOUNGE et al. (26) in 135 patients with carcinoma in situ, and 39.8 years by Ross and CUYLER (16) in 52 patients with intra-epithelial carcinoma.

In all cases of »epithelial hyperplasia with nuclear abnormalities: non-invasive carcinoma» and »borderline cases with doubtful frank invasion», further sections were made from the original blocks to reveal possible changes, especially invasive growth not visible on the primary sections; these re-examinations did not result in findings calling for any alteration in the original histologic diagnoses.

The group *simple epithelial hyperplasia* comprises almost one-half of the cases, or 50 patients in all. The age distribution, ranging from 22 to 68 years (mean age 40.1 years), of these patients will be seen from Diagram 2. The great majority of the cases have been kept under observation only, except that in 3 cases electro-coagulation of the affected part of the portio mucosa was performed. Clinically, these changes are most frequently described as »erosions», and only in one case has the term »leukoplakia» been used. In 2 patients, biopsies performed 2 months and

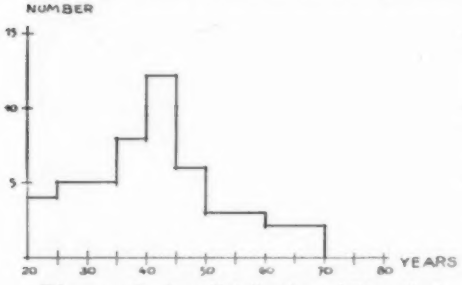


Diagram 2. Age distribution of 50 patients with simple epithelial hyperplasia.

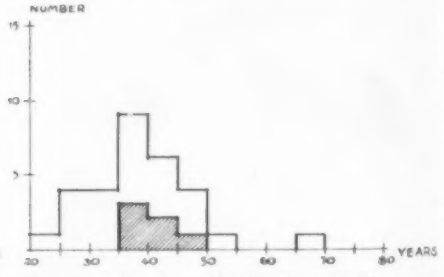


Diagram 3. Age distribution of 30 patients with epithelial hyperplasia with nuclear abnormalities: non-invasive carcinoma. Hatched areas denote those cases in which histologically demonstrable cancer developed within the period of observation.

4 years respectively after the first examination, revealed the presence of epithelium with distinct nuclear abnormalities. In both cases the changes evidently regressed spontaneously; at all events later examinations failed to demonstrate them. It is a noteworthy feature that none of the patients in this group developed cancer within the follow-up period.

30 patients on first examination presented epithelial changes which histologically have been designated as *epithelial hyperplasia with nuclear abnormalities: non-invasive carcinoma*. The age distribution is shown in Diagram 3. The mean age of this group was 38.7 years, the youngest patient being 22 and the oldest 67 years. In one case electro-coagulation of the suspicious area of the portio mucosa was performed, while the other cases were kept under observation. One patient was given radium treatment following 11 months observation. The clinical picture corresponding to the histologic findings was also atypical in most but not all of these patients; areas of erosion, sometimes with the words: »irregular» or »suspicious» added, were described. In 3 cases »whitish coats» or »leukoplakic patches» were reported. In 6 patients, development of cancer was noted later.

Finally, in 24 cases a histologic diagnosis of *borderline cases with doubtful frank invasion*, was made on tissue specimens removed when the patients were first seen at the Radium Centre. The age distribution varying from 26 to 62 years, is shown in Diagram 4 (mean age 40.3 years). In this as in the two former groups, the clinical finding in most but not all cases was atypical »erosion-like»; in addition one case had leukoplakia. In 2 patients the so-called erosion was treated with electro-coagulation, in one case an amputation of the portio was performed, and in one case electro-coagulation followed later by amputation of the portio was carried out. The other patients were kept under observation. In none of the cases submitted to local treatment was cancer subsequently observed. In 8 cases definite infiltrating growths were later observed.

The question as to the stage in which the cancerous condition, developing from one of the changes under review, after having been under observation for a longer or shorter period of time, is actually recognized,

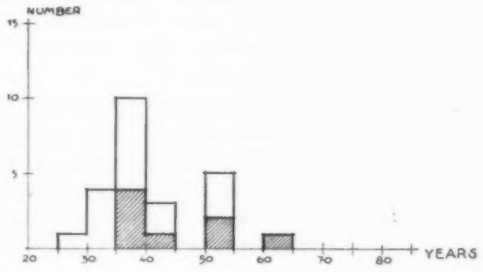


Diagram 4. Age distribution of 24 patients borderline cases with doubtful frank invasion. Hatching denotes those cases in which histologically demonstrable cancer developed within the period of observation.

is of course a decisive factor in the inherent problems of responsibility in taking up an attitude of expectancy.

If the patient's chance of a permanent cure has been considerably lessened, this will, of course, weigh heavily in favor of more active measures. Of the 14 cases of histologically demonstrable cancer observed among the 54 cases with abnormalities of the nuclei, twelve were in Stage I. Of these 12 patients, 8 were treated by radium on the histologic findings without clinical support for the diagnosis; 3 on positive histologic but doubtful clinical findings, while one received treatment by reason of both positive clinical and histologic diagnoses. One patient was in Stage II, and 1 in Stage III. The last-mentioned two cases call for a somewhat more detailed explanation. One (No. 38136) was that of a 38-year-old woman who had been referred to the Radium Centre in 1945 with a diagnosis of cancer of the rectum. No signs of rectal cancer were found, but a gynecologic examination showed »a bleeding area of erosion, 2 cm across, not typically malignant, around the cervical orifice». The patient had no gynecologic symptoms. A section removed from the area showed epithelium with considerable nuclear abnormalities but no invading growth. Curettage of the cervical canal was not carried out. The patient failed to return for further examination. In 1950, the patient was admitted to another hospital with cervical cancer, Stage II. The other case (No. 25172) was that of a 41-year-old woman who had sought medical advice for menostasia two months prior to being referred to the Radium Centre. At the first examination the »mucosa around the orifice was somewhat darkened and the lower margin of the posterior lip somewhat irregular». A section was removed from the suspicious area and a microscopic examination revealed: »Cervicitis, no signs of cancer». A second biopsy two months later showed »erosion with undifferentiated epithelium, suggestive of cancer». Biopsies carried out during the next two years revealed pronounced cell abnormalities but there was no evidence of definite infiltration. In this case also, curettage of the cervix was not carried out at any period. The patient failed to return for examination until 1945 (two years later) when she again visited the Radium Centre because of bleeding of about a month's duration. The finding was cancer in Stage III. In both cases blame may be attached to the Centre for failing to take cervical scrapings and to the patients for lack of co-operation.

Of 54 patients with portio epithelium presenting pronounced nuclear abnormalities, 16 had clinical and histologic regression of the changes within the follow-up period, 15 cases showed clinical regression only; in these cases, however, biopsies were only performed in the early part of the follow-up period and hence it is not possible to state whether the epithelium had become normal at the same time as regression had oc-

curred. Three cases remained clinically as well as histologically stationary and 3 of the patients could not be traced. Lastly, as already mentioned, in two cases amputation of the portio was carried out, and one case was submitted, after 11 months' observation, to radium therapy.

In the group »epithelial hyperplasia with nuclear abnormalities: non-invasive carcinoma», intervals of 25, 25, 26, 29, 42 and 62 months elapsed between the time when mucosal changes were first noted and the development of cancer. The last figure was obtained in the case of one of the two patients who failed to return for re-examination and was eventually admitted to hospital elsewhere; it is therefore hardly reliable. In the group »borderline cases with doubtful frank invasion», the corresponding periods were 5, 13, 17, 26, 27, 29, 47 and 67 months respectively. The figure of 47 may also not be a reliable one in as much as the patient concerned appeared after two years, having missed the intervening control appointments.

Discussion

In considering certain intra-epithelial mucosal changes in the portio vaginalis in the present work, differentiation is made between two main groups — cases with and without abnormalities of the nuclei. The latter comprises cases described in the present work as simple epithelial hyperplasia — a simple thickening of the epithelium, without cytologic deviations from the normal. These cases may be ignored when the problem is the possible subsequent development of cancer. 25.9 per cent of the cases in the other main group, comprising what in this paper has been termed »epithelial hyperplasia with nuclear abnormalities: non-invasive carcinoma» and »borderline cases with doubtful frank invasion», developed histologically demonstrable cancer of the uterine cervix in from 5 to 67 months. It had not been possible to foretell from the histologic or clinical picture which cases would eventually become malignant. A certain difference in age was evident in the two categories and the development of cancer within the period of observation was observed only in those patients who were over 35 years at the first examination. As regards treatment the age may influence us since in the younger patient the tendency will naturally be to keep her under observation while in the older subject, especially the postmenopausal woman, a more active procedure may be warranted. The sequelae of treatment, more particularly sterility resulting from radical surgery, are naturally of less importance in this age group. The adequacy of more limited procedures (electro-coagulation, amputation of the portio) designed to prevent a later development of cancer, cannot be judged from the very small number of cases in the writer's material. How frequently the patients whom it

has been decided to keep under observation, should return for examination is a question of the utmost importance. From the latent periods in the present material, where the shortest period of time elapsing between the finding of intra-epithelial nuclear abnormalities and the development of frank cancer was 5 months, the interval between repeat examinations should not exceed 3—4 months. In deciding upon expectant treatment one will be influenced by the probability of the patient returning for the control examination at the appointed times. If such regular controls are carried out, we may feel fairly confident that the chances of cure will not have been appreciably diminished. As already mentioned, cancers which developed from the epithelial changes which form the subject of this paper, were in Stage I in the case of patients observed regularly, and in $^2/_3$ of the cases diagnoses were in fact only made by microscopic examination. The two more advanced cases of cancer of the uterine cervix were found in patients who failed to return for examination for 2 years and 5 years respectively.

Conclusions

Of 104 patients with supposedly precancerous changes of the mucosa of the portio, 14 (13.5 %) developed cancer within an observation period ranging from 5 to 12 years.

The mean age of all patients on first examination at the Radium Centre was 40.2 years. No significant difference in the mean age was found in the three groups into which the material has been divided.

There was no development of cancer in any of the cases in the group »simple epithelial hyperplasia». In 30 patients in the group »epithelial hyperplasia with nuclear abnormalities: non-invasive carcinoma» cancer developed in 6 (20 %) in from 25 to 62 months. Of 24 patients with epithelial changes designated as »borderline cases with doubtful frank invasion» 8 (33 %) were found to be suffering from cancer in from 5 to 67 months. None of the patients under 35 years of age at the first examination developed cancer within the period of observation.

It has not been possible to give a prognosis in individual cases from the histologic and clinical pictures.

If frequent repeat examinations (every 3 to 4 months) can be carried out, an expectant attitude regarding observation of the changes in the mucosa of the portio will be permissible and advisable, especially in the case of youngish patients (under 35 years). In women at or after the menopause, more radical procedures (total hysterectomy or radium therapy) may be considered but in these cases too, the patient's chances will probably not be diminished by waiting for some months, during which period histologic control must be maintained.

SUMMARY

The author surveys the diagnosis and treatment of the so-called »pre-canceroses» of the portio vaginalis and presents a material of 104 cases from the Radium Centre, Copenhagen. Three groups of changes, based upon histologic assessment, are described. The age-groups affected and the development of cancer are discussed in relationship to the prognosis. It is suggested that an expectant attitude may reasonably be adopted in most cases and will not prejudice the patient's chances, provided that frequent histologic control be exercised.

ZUSAMMENFASSUNG

Der Verfasser gibt einen Überblick über die Diagnose und die Behandlung der sogenannten »Praecancerose» der Portio vaginalis und legt ein Material von 104 Fällen aus dem Radiumzentrum in Kopenhagen vor. Es werden 3 histologisch verschiedene Gruppen beschrieben. Die betroffenen Altersgruppen und die Entwicklung des Krebses werden in ihrer Beziehung zur Prognose diskutiert. Es wird vorgeschlagen, in den meisten Fällen eine abwartende Haltung einzunehmen; man sollte keine vorausgesetzte Meinung über die Chansen der Patienten haben, vorausgesetzt, dass häufige histologische Untersuchungen vorgenommen werden können.

RÉSUMÉ

L'auteur résume le diagnostic et le traitement des états précancéreux de la portion vaginale du col de l'utérus et présente 104 cas provenant du Centre du Radium de Copenhague. L'examen histologique permet de décrire trois groupes de lésions. L'auteur étude le pronostic en fonction de l'âge et du développement du cancer. Il suggère que dans la plupart des cas, on peut rester dans l'expectative, sans diminuer les chances de la malade, à condition de faire des contrôles histologiques fréquents.

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FROM THE RADIUM CENTRE (DIRECTOR: JENS NIELSEN), COPENHAGEN, DENMARK.

ROENTGEN THERAPY IN CANCER OF THE EXTRATHORACIC PORTION OF THE OESOPHAGUS

by

Bertel Jørgsholm

Introduction

Recent progress in surgery has opened up the possibility of radical operation in the treatment of oesophageal carcinoma. If the patient is a good surgical risk and the tumour not too far advanced, the surgeon does not meet insurmountable difficulties in dealing with the intrathoracic, or, more correctly, the lower portion of the oesophagus, but the surgical treatment of carcinoma affecting the upper, extrathoracic portion is still an extremely difficult and dangerous undertaking. However, discussions in recent years appear to show that serious attempts are being made at tackling the problem surgically.

We, therefore, thought that it might be of interest to show what has been achieved within this field by radiological treatment. It must be borne in mind that while the indications for surgical treatment of carcinoma affecting the upper portion of the oesophagus are extremely narrow and depend on the patient's condition and the spread of the growth, the indications for radiotherapy are usually much wider and the radiologist's subjects therefore poorer risks. Any comparison of the results must, therefore, be made with due regard to these factors.

The majority of previous radiological reports on carcinoma of the oesophagus have been confined to the intrathoracic portion of the oesophagus, since several workers, for radiotechnical reasons, classify carcinoma of the cervical or extrathoracic portion of the oesophagus as carcinoma of the hypopharynx, inter alia. In this connection, a considerably better prognosis for carcinoma of the latter site is often reported; up to 20 per cent 5-year survivors have been mentioned (BUSCHKE and CANTRIL,

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ZUPPINGER). With a few exceptions, however, the clinical results are not up to these expectations which appear to be fulfilled only with regard to the upper part of the hypopharynx (or in selected materials).

In a paper on hypopharyngeal carcinoma, COUTARD in 1935 included carcinoma of the pharyngeal opening of the oesophagus. He reported 12 per cent 5-year survivors (11 patients) following prolonged fractionated irradiation of 89 patients, but stated that since carcinoma of the lower portion of the hypopharynx and around the pharyngeal opening of the oesophagus was apt to infiltrate the surrounding muscles, it was not so easily accessible to radiotherapy and therefore had a poorer prognosis. BACLESSE in 1949 arrived at the same conclusion in an analysis of all the cases treated by COUTARD and himself during the period 1921—42. The total series comprised 425 patients with a 5-year cure rate of only 6 %, or 27 patients. Among these 27 patients, only two had had cancer of the lower portion of the hypopharynx as compared with 63 % in the original material.

A few authors even go so far as to consider radiotherapy useless in such cases (ACKERMAN and REGATO).

Carcinoma of the pharyngeal opening of the oesophagus is also included in AHLBOM's (1941) series of hypopharyngeal carcinoma derived from the period 1930—1939. At the end of 5 years he had 6 per cent survivors from among 150 patients treated with roentgen rays, teleradium, or a combination of the two.

In a recent publication FOLKE JACOBSSON has reported that during the period 1939—42, the 5-year cure rate for low-seated carcinoma of the hypopharynx *treated* at Radiumhemmet, Stockholm, was 5 per cent. After the technique was altered in 1943 to include fluoroscopic control of each treatment and the fields were diminished (3.3—4 × 10—15—20), the results improved, and now the 5-year cure rate for this form of carcinoma is 17 % or 10 out of 56 patients *treated* during the period 1943—45. It is stated by AHLBOM as well as JACOBSSON that a 5-year cure rate of about 20 % may be expected following optimum irradiation with 200 kv., *i. e.* a tumour dose of 5,700—6,200 r.

In Sweden low-seated hypopharyngeal carcinoma makes up 75 % of all malignant growths in the hypopharynx and occurs in females in 60 % of all cases. This female preponderance appears to be related to the common occurrence of the Plummer Vinson syndrome among the female rural population in Sweden. It is difficult to decide whether the relatively favourable Swedish results are due to improved technique or to the said phenomenon, but it is worth mentioning that in BACLESSE's material only 1 % were females.

A few authors include the entire oesophagus, but often the results for each part are not stated separately. In JENS NIELSEN's paper (1940) each

section is analysed separately, and my investigation constitutes a continued analysis of this material which, since that time, has increased. In JENS NIELSEN's four patients who were alive sign-free 3—7 years after roentgen irradiation, the growths had been confined to the upper extrathoracic portion of the oesophagus. (These cases are included in the present series.)

On the whole, the results for the cervical portion of the oesophagus appear to be only slightly better than those reported for the intrathoracic portion. In this connection let me refer to FLEMING (1947) who reviewed the results reported by 10 workers from a total of 800 patients followed up for 5 years and treated with various forms of radiotherapy. Only 10 out of these 800 patients were living at the end of 5 years. FLEMING also concluded that the results, which covered the entire oesophagus, were somewhat better for the upper third.

Without considering the various forms of irradiation, the writer finds that on the whole fractionated prolonged roentgen therapy appears to give the best palliative results and to cause the least subjective discomfort. (This method causes less damage to the normal tissues, secondary radiation changes appear to be less marked, and the risk of secondary irradiation carcinoma appears to be less than following a briefer course of heavy radiation. On the other hand, it is doubtful whether the length of treatment has any influence on the sterilization of the cancer.) Intraoesophageal treatment with radium passed down in a bougie, which has been practised mainly by GUISEZ with remarkable results, seems to be unsuitable in several respects and has been abandoned in most clinics. GUISEZ' figures also do not appear to be quite reliable (microscopic verification and exact situation are not available in all cases) and similar results have not been obtained by this method in the hands of other workers (ZUPPINGER and others).

Treatment with teleradium is used by several workers and appears to afford satisfactory palliation (LEDERMAN and CLARKSON 1945). Million voltage units do not seem to have improved the results (WILLIAMS 1948). For details regarding roentgen rotation therapy, the advantages of which are most conspicuous in the treatment of the intrathoracic portion of the oesophagus, the reader is referred to JENS NIELSEN.

Despite the technical advances of recent years, resection of the cervical portion of the oesophagus has resulted in only a few 5-year survivals. In addition to the case, living at the end of 7 years, reported by WATSON in 1949 the literature contains only ARTHUR EVANS' patient, living at the end of 23 years (1934), and VILFRED TROTTER's patient, alive at the end of 10 years (1937). Several workers have been able to report survivors free from signs 1—3 years after resection, but it is the general impression that the patients, even after successful operations, succumb to recurrence

or metastases 6 months to 2 years after operation. In an attempt to find the reason for these poor results, SHEFTS and FISHER (1949) advocated bilateral, radical dissection of the cervical lymph nodes in all resections for carcinoma of the cervical portion of the oesophagus.

Material

During the period 1931—1944, inclusive, a total of 452 patients with oesophageal carcinoma were referred to the Radium Centre in Copenhagen. In 109 cases the growth affected the extrathoracic portion of the oesophagus, *i. e.* the part from the pharyngeal opening down to the level of the jugular notch. No patient was refused and the material therefore includes a number of intractable and desolate patients who died shortly after they were first seen or admitted. Of these 109 patients, 47 were females and 62 males (43.1 % females and 56.9 % males). The average age for the entire series was 63.5 years; the females averaged 59.5 and the males 67.3 years of age. (The age distribution is set out in Diagram 1 which shows also that the majority of the females belonged to a somewhat younger age group — 55—70 years, and the males — 60—75 years. The youngest patient was a 31-year old female and the oldest a male, aged 82.)

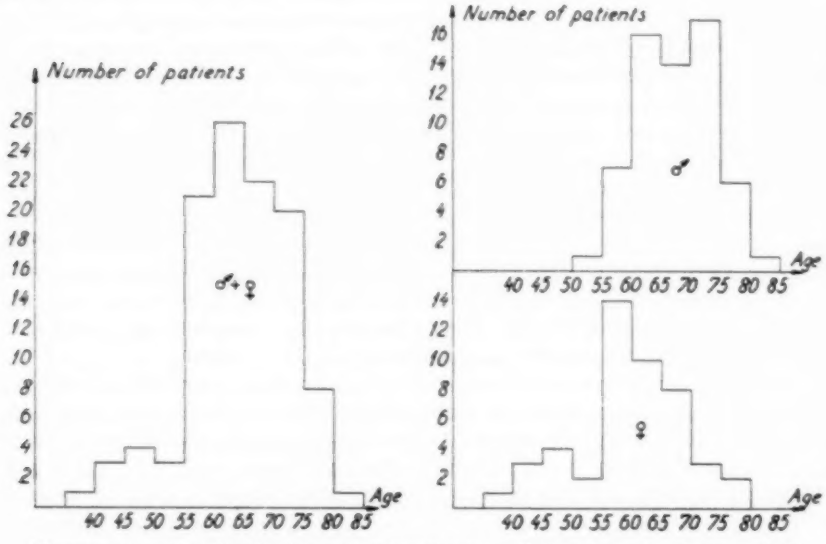


Diagram 1. Age distribution of 109 patients suffering from carcinoma of the extra-thoracic portion of the oesophagus.

Duration of symptoms

The duration of symptoms before the patient sought medical advice averaged 3.1 months, ranging from a few days up to more than 1 year. The duration of symptoms before the correct diagnosis was made and the patients referred to the Radium Centre averaged 4.6 months, ranging from 0.5 month up to more than 1 year. The time wasted is due to the fact that quite a large number of patients were treated first by their own physician by sedatives, painting of the throat, and bouginage, since early diagnosis is often extremely difficult.

Symptoms

In 106 cases (97 %) the symptoms were increasing dysphagia, first of solids, but later also for semifluids, increasing to complete stenosis in a few instances. Major or minor loss of weight occurred in 76 cases (70 %). Fifty-five patients (50 %) had pain in the throat with or without relation on swallowing. Hoarseness was a sign in 32 (29 %), increased secretion of mucus and regurgitation in 37 (34 %), and cough upon swallowing in 22 (20 %).

Site and extension of the tumour

The site and extension of the tumour were ascertained by roentgen examination, oesophagoscopy, and laryngoscopy. In this connection it is worth mentioning that the best films are obtained in the lateral view, with the casette supported by the patient's shoulder, at a focal-film distance of 150 cm.

In 52 instances the tumour was situated at or in the vicinity of the pharyngeal opening and was demonstrable in part by laryngoscopy, whereas the films in all cases except one showed a stricture or the outlines of a tumour from 1 to 10 cm down in the oesophagus. For this reason they were classified as oesophageal carcinomata although it is open to discussion, whether a few originated primarily from the hypopharynx or from the oesophagus. Fig. 1 shows the situation of the tumours situated at the oesophageal open-

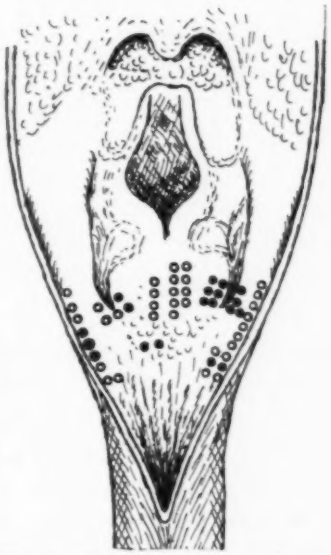


Fig. 1. Graphic representation of the site of the tumours at the oesophageal opening or arising from the oesophagus, visible by laryngoscopy.

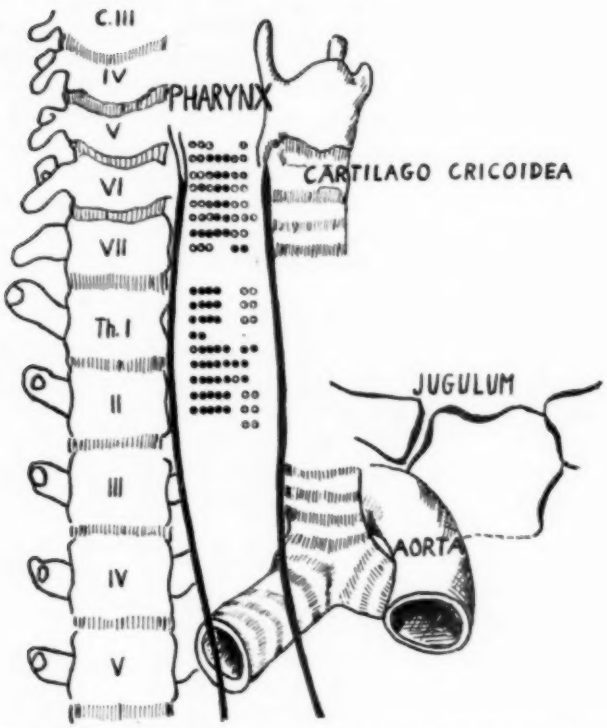


Fig. 2. The approximate location and level of all 109 tumours in relation to the vertebral column, the cricoid cartilage, and the jugular notch (● = ♂; ○ = ♀).

ing or arising from the oesophagus and visible by laryngoscopy. The majority or *63 per cent* occurred in women and were at the typical post-cricoid site. Fig. 2 is a graphic representation of the level of all the tumours in relation to the vertebral column, the cricoid cartilage, and the jugular notch. There is an accumulation or *75 per cent* of growths in males on a level with the jugular notch. The size of the tumours, estimated in the roentgen films, ranged from 1—14 cm (1—2 cm, 23 patients, 2—5 cm, 40 patients, 5—9 cm, 34 patients, 10 cm and more, 10 patients). One patient was not examined roentgenologically because of poor general condition, but autopsy revealed a carcinoma of the oesophagus. In another case the films showed nothing abnormal, but oesophagoscopy revealed a tumour on the posterior wall of the gullet.

Metastases

Metastases were present at the first examination in 44 cases (40 %) (22 males and 22 females), mainly in the form of palpable cervical and supraclavicular lymph nodes. Microscopic proof, however, was obtained in only a few cases. Four patients also exhibited pulmonary metastases, affecting both lungs in 2 cases, and one had metastases in the ribs and pleurae.

Autopsy

Autopsy, performed in 47 cases, revealed metastases in 20 (43 %), mainly in the form of extension to the para-oesophageal, mediastinal, supraclavicular, and cervical lymph nodes. In 7 instances metastases were found in the lungs or pleurae, in 2 cases in the liver, and in 1 case in the right elbow as well in the lungs and pleurae. In one case the metastatic deposits were in the thyroid gland. Most of the patients died in a state of extreme cachexia with terminal pneumonia.

If the clinical findings of metastases in cases in which autopsy was not performed is also taken into account, the total number of patients exhibiting metastases at death is 54 or 49.5 %.

Microscopical examination

In 87 cases (80 %), the roentgen diagnosis was verified by microscopical examination. In 3 additional patients the diagnosis was proved by autopsy. In 19 cases, microscopical examination was not performed or gave negative results, but in these cases the clinical course left no doubt about the diagnosis, 18 of the 19 patients dying within 18 months of admission (13 with metastases) and 1 with metastases at the end of 23 months. The microscopical examinations are shown in table 1, which

Table 1

The microscopical diagnosis in 87 cases of carcinoma of the extrathoracic portion of the oesophagus

				Alive at end of 2 years			Alive at end of 5 years		
	♂	♀	♂+♀	♂	♀	♂+♀	♂	♀	♂+♀
Parakeratotic squamous-cell carcinoma ...	21	22	43	2	4	6	2	2	4
Squamous-cell carcinoma of the mucosal type	16	15	31	2	4	6	1	3	4
Basal-cell carcinoma	6	0	6	1	0	1			
Cylindrical carcinoma	3	0	3						
Adenocarcinoma	1	0	1						
Squamous-cell carcinoma of the Bowen type	0	1	1						
Unspecified carcinoma (metastases)	2	0	2						

also gives the microscopy for the 2- and 5-year survivors. These small numbers do not suggest any correlation between the grade of differentiation and the curative effect of irradiation.

Treatment

The treatment was individual, and standardization was neither tried nor planned. It is, therefore, difficult to tabulate the treatment, but its principle was fractionated prolonged roentgen therapy.

(1) No treatment was attempted in the case of 3 patients who were desolate on admission and died shortly afterwards.

(2) Seventeen patients received only small palliative doses, most of them merely *solaminis causa*. In a few others a more energetic treatment was planned, but had to be given up as the patients deteriorated and proved unable to stand the treatment. The palliative tumour dose ranged from 150—1,500 r. All these patients, except two, died within one month of the onset of treatment. The remaining two, who had undergone gastrostomy, survived for 3 and 6 months respectively.

(3) Twenty-two patients received larger palliative doses, the total dose on the tumour ranging from 1,500 to 3,000 r administered in the course of 10—55 days. A few patients with tumours on a level with the jugular notch received palliative rotation therapy, the total dose ranging from 800—3,000 r, administered for 7—50 days. The average survival time for these 22 patients was 2.9 months.

(4) Sixty-seven patients (37 males and 30 females) received a complete fractionated roentgen treatment, *i. e.* an effective attempt at attacking the tumour. Metastatic activity in 25 of the patients, however, reduced this treatment to a mere palliative measure. The calculated total tumour dose ranged from 3,200—10,200 r administered in the course of 21—98 days, through $^1/_2$ mm of copper or a Thoraeus filter, focal-skin distance 50—70 cm, 165—180 kv. to 2—7 fields (6 × 8 to 10 × 15 cm). The daily dose was 100—200 r in 1 or 2 daily sessions. Eight of the patients (7 males and 1 female) with tumours at a level with the jugular notch received rotation therapy, the total tumour dose varying from 4,500—9,500 r administered in the course of 25—50 days, the axis field varying from 6 × 3 to 10 × 6 cm, focal-axis distance 50 cm, filter $^1/_2$ mm of copper, 180 kv.

The time at which treatment was terminated was determined by clinical observation, roentgen evidence of the reaction of the tumour, and the patient's general condition. Diagram 2 gives the relation between the total tumour dose and the period of treatment set out in a co-ordinate system in which the number of roentgens is the ordinate and the duration of treatment in days the abscissa.

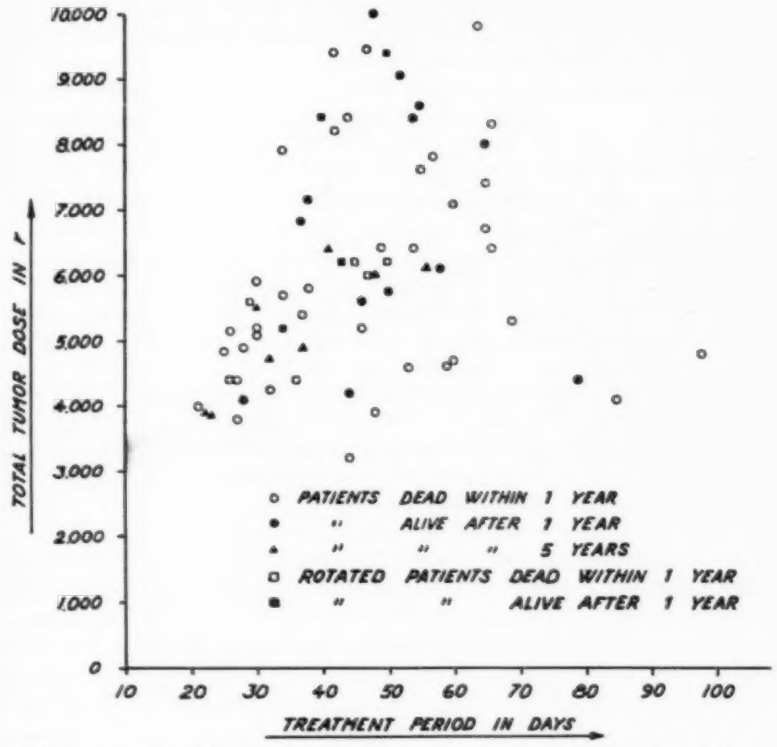


Diagram 2. Graphic representation in a co-ordinate system of the relation between the total tumour dose in roentgens and the treatment period in days for 67 patients with carcinoma of the extrathoracic portion of the oesophagus.

Results

At the end of one year 18 patients were alive and symptom-free, whereas 7 were alive with symptoms from the growth, 83 had died from the oesophageal carcinoma and 1 from another cause (1 male with carcinoma of the prostate gland and metastases in the bones died 7 months after treatment was started; autopsy failed to show signs of oesophageal carcinoma). At the end of two years 11 were symptom-free, 2 alive with carcinoma of the oesophagus, 93 had died from the carcinoma and a further 2 from other causes (1 man died from pneumonia 21 months after the onset of treatment, but showed no post-mortem evidence of oesophageal carcinoma, and 1 woman died from heart disease 23 months after

Table 2

The distribution of 109 patients with carcinoma affecting the cervical portion of the oesophagus 1—5 years after the onset of treatment

At the end of	Alive symptom-free			Alive with symptoms			Died from oesophageal carcinoma			Died from other causes		
	♀	♂	♀×♂	♀	♂	♀×♂	♀	♂	♀×♂	♀	♂	♀×♂
1 year	8	10	18	2	5	7	37	46	83	0	1	1
2 years	7	4	11	1	1	2	38	55	93	1	2	3
3 years	6	4	10	1	0	1	39	56	95	1	2	3
4 years	5	3	8	1	0	1	39	57	96	2	2	4
5 years	5	3	8	0	0	0	40	57	97	2	2	4

treatment; no autopsy was performed, but she had no oesophageal symptoms at death). At the end of three years 10 patients were alive and symptom-free, 1 alive with cancer, and 95 had succumbed to oesophageal carcinoma. At the end of four years 8 were symptom-free, 1 alive with cancer, 96 had died from oesophageal carcinoma and further 1 from another disease (1 female succumbed to coronary thrombosis 4 years after treatment; autopsy revealed no signs of oesophageal carcinoma). The 5-year result is 8 patients alive and symptom-free, whereas 97 had succumbed to carcinoma of the oesophagus and 4 to other diseases.

Diagram 3 gives the survival curve for all 109 patients. The characteristic feature is the large number of deaths during the first few months. At the end of 5 years 8 patients or *7.3 %* are still alive without symptoms

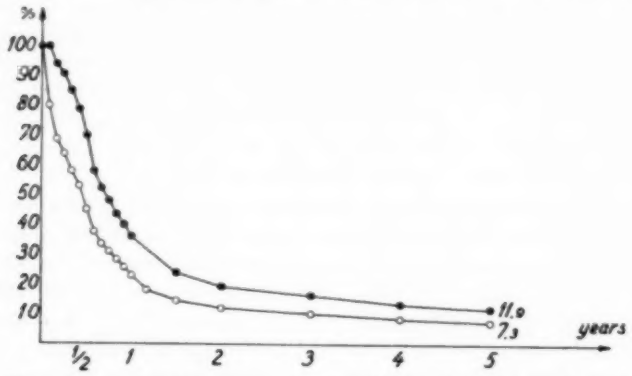


Diagram 3. Survival curve (○) for 109 patients (treated and untreated) with carcinoma of the extrathoracic portion of the oesophagus, and survival curve (●) for 67 patients who received a complete treatment.

of cancer. The same figure gives the survival curve for the 67 patients who received complete treatment. Among them, however, 25 or 37.3 % exhibited nodal metastases prior to treatment. The survival time for these 25 patients averaged 7.6 months from the onset of treatment.

Among the eight patients surviving at the end of 5 years the following 5 died later from intercurrent diseases: (1) 1 male died from pneumonia about 6 years after treatment; autopsy showed no signs of oesophageal carcinoma. (2) 1 male died from unknown cause 15 years after treatment; no oesophageal symptoms at death. (3) 1 male died $12^1/_4$ years after treatment from a new carcinoma, in the middle portion of the oesophagus, arising 10 years after the first growth. Rotation therapy relieved symptoms for $2^1/_4$ years, but he then developed a recurrence and pulmonary metastases to which he rapidly succumbed. (4) 1 female died from pneumonia 8 years after treatment and (5) another female succumbed to cirrhosis of the liver $13^1/_2$ years after treatment. In the last-mentioned case, autopsy showed no signs of cancer. The remaining 3 are still alive without symptoms 7, $7^1/_2$, and 11 years respectively after the onset of treatment.

Complications

In addition to poor general condition, often accompanied by fever, perforation of the oesophagus occurred in 17 patients. In the majority of the cases, viz. 12, this did not occur until after treatment, when recurrences appeared. In one case the perforation occurred prior to, and in 4 cases during treatment. In most of the cases the perforation was into the trachea, leading to aspiration pneumonia, in 6 cases into the mediastinum or the peri-oesophageal space leading to mediastinitis or cervical phlegmon.

Fifteen patients developed a more or less marked stridor (9 before, 2 during, and 4 after treatment, when recurrence appeared). Seven had to undergo tracheotomy (5 before and 2 after treatment because of recurrence). Paresis of the vocal cords occurred in 30 cases (22 before, 1 during and 7 after treatment).

Eighteen patients had to undergo gastrostomy (2 before treatment, 7 because of increasing dysphagia during the treatment, 8 after the treatment because of recurrence, and 1 seven years after treatment because of cicatricial stricture). Two additional patients with cicatricial stricture were treated with bougie (later both developed recurrence and died 18 and 8 months respectively after treatment). Thus, cicatricial stricture does not appear to have been particularly common in our series.

Radiation myelitis did not occur in any case.

The Plummer-Vinson syndrome, *i. e.* a pathological state characterized largely by sideropenia, occurred in only a few cases in its typical form.

It is almost only encountered in females, and according to AHLBOM it favours the development of carcinoma in the upper digestive tract, particularly in the hypopharynx and upper portion of the oesophagus.

In Sweden, where this syndrome is much more common, there is a corresponding preponderance of females suffering from carcinoma of the upper digestive tract. The studies of AHLBOM (1937), and VIDEBÆK (1944), showed that among all cases of carcinoma of the pharynx and oesophagus notified in Stockholm and Copenhagen, 48 and 23 per cent respectively were females. Moreover VIDEBÆK found the Plummer-Vinson syndrome in only $2^1/_2$ per cent of all female cases of carcinoma, affecting the upper digestive tract, in Copenhagen, whereas AHLBOM found 60—70 per cent in Stockholm. In the present series which comprises only the upper part of the oesophagus, 47 % were females, but only 6 patients exhibited symptoms suggesting Plummer-Vinson's syndrome and fewer still the typical picture of sideropenia, brittle nails, rhagades at the corners of the mouth, atrophy of the papillae of the tongue, and long-standing dysphagia.

Discussion and Conclusions

It is frequently emphasized that earlier recognition may improve the prognosis of these serious lesions. With regard to carcinoma of the cervical portion of the oesophagus, the failure of early diagnosis is associated with causes due both to the patient and physician. The first symptom is usually difficulty in swallowing, and since a slight degree of dysphagia is no uncommon sign of ordinary lesions, it is often neglected by the patient as well as the physician. But when the dysphagia has become constant and obstinate, the neoplastic processes are usually also fairly advanced. The only chance of early diagnosis is an extended use of roentgen examinations, laryngoscopy, and oesophagoscopy, *i. e.* specialist examinations, in all cases of dysphagia. But even though an early diagnosis is made, the response of these tumours to radiation differs widely.

As apparent from diagram 2, the 5-year survivors are grouped within an area limited by a total tumour dose ranging from 3,800 to 6,400 r and a period of treatment ranging from 22 to 56 days. Within, as well as outside, this area there are patients with apparently clinically and histologically uniform tumours who failed to respond favourably to the radiation or to exhibit a permanent cure.

If a conclusion is to be drawn from the series, it must be as follows: A certain small percentage of these growths appears to be radio-curable, even though they receive only a moderate tumour dose within a certain range of dosage. An increase in the tumour dose or the period of treat-

ment beyond the limits of this range does not increase the curability, but only the number of complications and the strain on the patient. Within the range, the curability appears to depend less on the maximum tumour dose than on the origin of the tumour, its manner of growth, extension, rate of metastatic activity, and on unknown radiobiological factors.

Consequently, an earlier diagnosis is tantamount to only a limited, but important aid in increasing the curability. It does not appear to be possible to establish a narrower range of optimum dosage for curable carcinomas, and the treatment must be individual.

Case Histories

Case 1. 6104. Male, aged 70. Referred to the Radium Centre on Apr. 25, 1930 with carcinoma of the uvula and palate. Micr. exam.: Squamous-cell parakeratotic carcinoma.

After roentgen therapy he remained symptom-free until 1933, when he developed carcinoma of the hypopharynx (arytenoid region and left pyriform sinus). Micr. exam.: Squamous-cell carcinoma of the mucosal type.

Roentgen therapy and symptom-free until 1936, when he re-appeared with dysphagia of one month's standing; roentgen examination revealed a stricture, 2—3 cm in length, with irregular contours immediately above the jugular notch. Oesophagoscopy showed a large, partly ulcerated tumour 20 cm from the front teeth. Micr. exam.: Squamous-cell carcinoma of the mucosal type. Treatment: 3 anterior fields, Thoraeus filter, focal-skin distance 70 cm, 180 kv., 4 ma. Total tumour dose 6,400 r/41 days.

The tumour subsided. Symptom-free for 5 months, after which another stricture developed and sudden dysphagia due to a foreign body occurred; the later was removed. Again symptom-free until October 1941, when the patient died from pneumonia at the age of 81 years, 6 years after treatment for oesophageal carcinoma.

Autopsy: No signs of carcinoma in the oesophagus or hypopharynx; right-sided pneumonia.

Case 2. 8651. Male, aged 65. Referred to the Radium Centre on Oct. 5, 1932. Pain on swallowing, hoarseness, and mucous sputum for previous 2 months. General conditions satisfactory. Roentgen examination showed an irregular contour in the upper portion of the oesophagus and enlargement of the space between the trachea and the vertebral column. Laryngoscopy and oesophagoscopy revealed a tumour far down the posterior wall of the larynx, extending into the right pyriform sinus. Micr. exam.: Parakeratotic carcinoma.

Received fractionated roentgen therapy, right and left cervical field, 11 × 13 cm, Thoraeus filter, focal-skin distance 50 cm, 165 kv. Total tumour dose 5,500 r/30 days.

During this treatment the tumour yielded completely, and only slight oedema of the right arytenoid region remained. After that, patient was symptom-free, but died 15 years after treatment from an unknown cause, without symptoms from the oesophagus.

Case 3. 8776. Female, aged 48. Referred to the Radium Centre on Nov. 2, 1932. For 4 months pain in the throat, for the previous month increasing dysphagia and regurgitation of mucus. Roentgen examination (Fig. 3) showed a filling defect, 4—5 cm in length, beginning at the pharyngeal opening of the oesophagus and anterior displacement and compression of the trachea. Laryngoscopy: Large ulcerated tumour at the

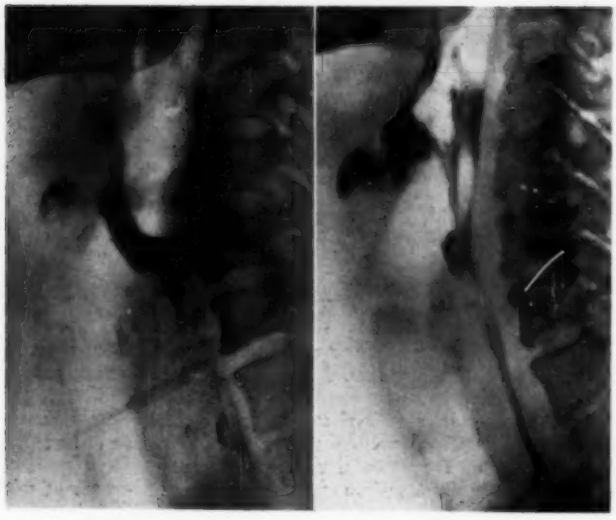


Fig. 3. Roentgen appearances in a case of carcinoma of the extrathoracic portion of the oesophagus before treatment and 8 months after fractioned prolonged roentgen treatment (Case 3).

bottom of the left pyriform sinus; left-sided paresis. Micr. exam.: Squamous-cell carcinoma of the mucosal type.

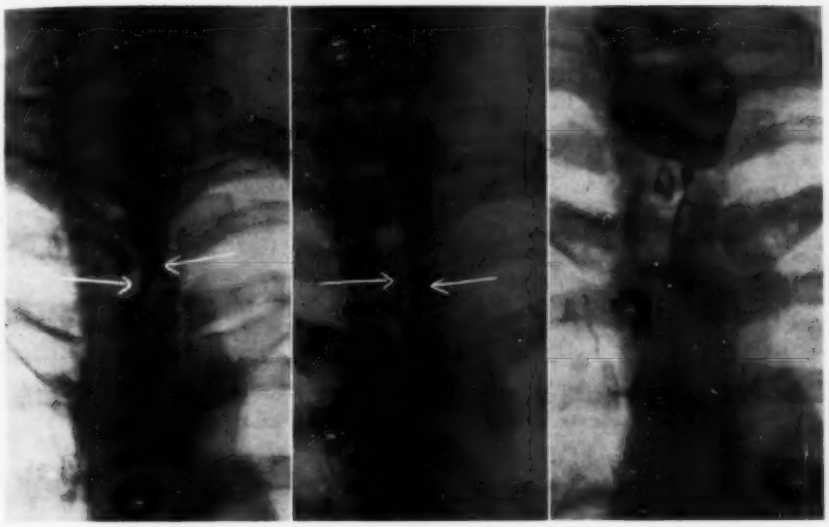
Treatment: Right and left lateral field, 8 × 10 cm, Thoraeus filter, focal-skin distance 50—52 cm, 165 kv. Total tumour dose 3,900 r/22 days. During the treatment the tumour yielded completely, as evidenced by radiography and by laryngoscopy. Symptom-free until August 1943, when cancer of the right breast developed. Preoperative roentgen therapy and radical operation. Patient had developed a low-degree myxoedema as a result of the radiation (B. M. R. — 12 %). Symptom-free until February 1945, when jaundice which was at first interpreted (erroneously) as a sign of hepatic metastases, occurred. Died from hepatitis in May 1946, 13¹/₂ years after treatment.

Autopsy: Chronic hepatitis; severe hepatic atrophy; no signs of carcinoma.

Case 4. 9275. Male, aged 58. Referred to the Radium Centre in March 1933. Pain on swallowing of 3 months' standing, hoarseness and increased secretion of mucus. Roentgen examination disclosed a tumour of the oesophagus extending from the lower portion of the posterior laryngeal wall to the level of the second dorsal vertebra. Laryngoscopy showed a neoplastic growth in the lower part of the posterior laryngeal wall. Micr. exam.: Squamous-cell carcinoma of the mucosal type.

Treatment: Right and left cervical field, 9 × 12 cm, Thoraeus filter, focal-skin distance 65—68 cm, 165 kv. Total tumour dose 6,100 r/56 days.

The tumour yielded completely to treatment. Symptom-free for 10 years, after which he developed increasing dysphagia. Roentgen examination revealed a tumour, 9 cm in length, in the middle portion of the oesophagus. Micr. exam.: Solid carcinoma.



A B C

Fig. 4. Roentgen appearances in a case of carcinoma of the extrathoracic portion o the oesophagus (A) before treatment, (B) after treatment; (C) 8 years after treatment showing a cicatricial stricture (with smooth contours). (Case 5.)

Rotation therapy, 4,000 r/24 days. The tumour yielded and the patient remained symptom-free for $2^1/_4$ years, when he developed a recurrence with pulmonary metastases, and died.

Case 5. 15117. Female, aged 31. Referred to the Radium Centre in November 1936. For several years mild dysphagia, worse about 1 year prior to treatment simultaneously with weight loss and fatigue. The patient was small, asthenic, pale, thin, and exhibited Plummer-Vinson's syndrome. Roentgen-examination (Fig. 4) showed a circular stenosis, 5 cm in length, with irregular contours, situated 6 cm below the pharyngeal opening of the oesophagus and extending to the jugular notch. Oesophagoscopy disclosed a circular, ulcerated constriction with raised edges 22 cm from the front teeth. Micr. exam.: Parakeratotic squamous-cell carcinoma.

Treatment: 2 lateral fields, 8×10 cm, Thoraeus filter, focal-skin distance 65—77 cm, 165—175 kv. Total tumour dose 5,000 r/37 days. After treatment the tumour became flattened, but there was still some degree of stricture. Oesophagoscopy: Stricture without signs of tumour. After treatment she felt well, but still had dysphagia due to a cicatricial stricture. Bouginage. In September 1944 gastrostomy because of cicatricial stricture; a plastic operation for the stenosis was contemplated, but never carried out. Died from pneumonia in May 1945, $8^1/_2$ years after treatment.

Case 6. 19744. Female, aged 61. Referred to the Radium Centre in February 1939. Dysphagia for about 3 months. Radiography showed a thickening of the posterior wall of the hypopharynx. Laryngoscopy revealed the upper border of an ulcerated tumour

in the posterior wall of the oesophageal opening. Micr. exam.: Squamous-cell carcinoma of the mucosal type.

Treatment: Right and left cervical field, 8 × 10 to 6 × 8 cm, Thoraeus filter, focal-skin distance, 72 cm, 180 kv. Total tumour dose 6,100 r/48 days.

The treatment resulted in a complete disappearance of the tumour, evidenced by radiography as well as laryngoscopy. During treatment, a brief period of aphonia. At a follow-up examination on Apr. 30, 1950, 11 years after treatment, the patient presented neither subjective nor objective signs.

Case 7. 24649. Female, aged 69. Referred to the Radium Centre in May 1941. Increasing dysphagia for previous 4 months. Weight loss and pain upon swallowing. Good general condition, slightly obese. Roentgen examination showed an enlargement in the space between the trachea and the vertebral column, compression of the trachea, and a filling defect in the upper portion of the oesophagus down as far as the jugular notch, with irregular, ragged contours. Laryngoscopy revealed necrotic ulceration deep down the posterior aspect of both arytenoid regions. Micr. exam.: Parakeratotic squamous-cell carcinoma.

Treatment: 3 anterior fields, 2 posterior fields, all measuring 8 × 10 cm, filter $^1/_2$ mm of copper, focal-skin distance 50 cm, 180 kv. Total tumour dose 4,000 r/22 days.

The treatment resulted in a complete disappearance of the tumour, evidenced by radiography and laryngoscopy. Symptom-free when last seen in October 1948, $7^1/_2$ years after the treatment, and alive at the time of writing.

Case 8. 30890. Female, aged 44. Referred to the Radium Centre in June 1943. For previous $2^1/_2$ months pain upon swallowing, no loss of weight. General condition good. Roentgen examination showed thickening of the posterior hypopharyngeal wall and irregular contours in the upper portion of the oesophagus. Laryngoscopy: In the midline, low down on the posterior wall a locket-shaped, flat area of ulceration with a depressed centre and eroded edges; lower limit not visible. Micr. exam.: Parakeratotic squamous-cell carcinoma.

Treatment: Right and left cervical field, 8 × 10 to 6 × 7 cm, Thoraeus filter, focal-skin distance 50 cm, 180 kv. During treatment the tumour disappeared completely. Total tumour dose 4,800 r/32 days. At the end of $4^1/_2$ years there was a slight oedema of the arytenoid region which persisted during the subsequent years. At a follow-up examination in April, 1950, 7 years after treatment, neither subjective nor objective signs present.

SUMMARY

To evaluate the roentgen treatment of carcinoma situated in the upper part of the oesophagus as far down as the level of the jugular notch, the author has collected and analyzed all the cases examined and treated in the Radium Center, Copenhagen 1931—1944. The series includes 109 patients, 67 of whom received a full course of fractionated roentgen treatment. The results are as follows: After 1 year, 18 patients were free from symptoms; after 2 years, 11 patients; after 3 years, 10 patients; after 4 years, 8 patients; and after 5 years, 8 patients.

ZUSAMMENFASSUNG

Zur Beurteilung der Röntgenbehandlung von Karzinomen im oberen Teil des Ösophagus bis herunter zum Jugulum sammelte und analysierte der Verf. alle derartigen Fälle, die während der Jahre 1931—1944 im Radiumzentrum in Kopenhagen untersucht

und radiologisch behandelt worden sind. Es handelt sich um 109 Patienten, von denen 67 vollständige fraktionierte Röntgenbehandlung erhielten. Die Resultate waren folgende: Nach einem Jahr lebten 18 Patienten symptomfrei, nach zwei Jahren 11, nach drei Jahren 10, nach 4 Jahren 8 und nach 5 Jahren 8 Patienten.

RÉSUMÉ

Pour juger la valeur de la roentgenthérapie des cancers de l'œsophage situés au dessus et au niveau du confluent jugulaire, l'auteur a rassemblé et analysé tous les cas examinés et traités au Centre du Radium de Copenhague, de 1931 à 1944. La série comprend 109 malades, dont 67 ont eu une série complète de séances de roentgenthérapie fractionnée. Les résultats sont les suivants: Au bout d'un an 18 malades ne présentaient aucun symptôme; au bout de 2 ans, 11 malades; au bout de 3 ans, 10 malades, au bout de 4 ans, 8 malades et au bout de 5 ans, 8 malades.

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BOOK REVIEWS

THE UTERINE CERVIX AND ISTHMUS UNDER NORMAL AND PATHOLOGICAL CONDITIONS. A CLINICAL AND ROENTGENOLOGICAL STUDY. By Jan Asplund. 76 pp, 60 illustrations. Acta radiol. Suppl. 91, Stockholm 1952. Sw. Kr. 20: —.

In view of the fact that little attention appears to have been paid up to now to the roentgenographic appearances of the uterine cervix and isthmus, more than 1,000 hysterograms were critically studied with special consideration to (1) the appearance of the cervix and isthmus, (2) the possibility of correlation between the roentgen findings and the clinical history. It was evident that very satisfactory films may be obtained provided that suitable instrumentation and a sufficiently viscous opaque medium are employed.

The normal radiographic appearances of the cervix vary considerably and may be briefly described as follows: The cervix is spindle- or pear-shaped and flattened anteroposteriorly; as a rule, the outlines of the walls are uniformly serrated, a pattern produced by the plicae palmatae. The width of the cervix and the pattern of the cervical mucosa often show variations during the menstrual cycle; the cervix is usually wider in the proliferative phase than in the secretory phase, and the serrated pattern of the mucosa is more marked in the former period.

The isthmus was outlined distinctly in about half of the hysterograms studied. It was usually cylindrical in shape, varied in length and breadth, but was always obviously narrower than the cervix and corpus uteri. The width of the internal os showed variations during the menstrual cycle; in the proliferative phase it was much wider than in the secretory phase; its dilatability was also greater in the former period. The suggestion is offered that the variations in width are due to changes in tone and apparently occur between the 13th and 16th day of the cycle, *i. e.* at the time at which ovulation generally occurs. Endocrine therapy influenced the width of the internal os; it became wider following the administration of oestrogen and narrower after progesterone.

Hysterograms of the pregnant uterus made at different stages of pregnancy revealed that the cervix and isthmus had much the same appearances as those of the non-pregnant uterus, though both structures were generally markedly lengthened. Up to the 6th month of pregnancy there was no roentgenologic evidence of an unfolding of the isthmus, which, according to earlier studies on anatomical specimens, is said to occur between the first and second trimester of pregnancy.

Special attention was paid to roentgenographic appearances of the cervix and isthmus which departed from the normal, and the possibility of correlating abnormal roentgen findings and the clinical history was investigated. There was no evidence of a relationship between the roentgenographic and microscopic appearances of the cervical mucosa. It was therefore felt that a diagnosis of cervicitis could not be made from the hysterogram alone. In some cases the folds of the cervical mucosa ran longitudinally towards the isthmus. This observation was relatively often made in cases in which the patient had previously had gonorrhoea, and in cases of tuberculous salpingitis or endometritis. It would seem that this pattern may be produced by cicatrization in the submucosa, the cicatrices being the results of trauma or inflammatory processes.

A narrow internal os was often observed in cases in which an operative dilatating procedure affecting the region of the isthmus was followed by infection. It was found that the frequency of a narrow internal os in cases of dysmenorrhoea was not greater than in

cases without a history of painful menstruation; nor was the dilatability of the internal os less than in the control cases. From this observation it would appear that a spasm in this region is not a constant feature of dysmenorrhoea. A remarkably wide internal os was found in cases of cystic glandular hyperplasia. The same observation was made in the presence of submucous myomata and polypi, particularly in cases in which the growths were situated in the lower part of the uterus. The internal os was also extremely wide in cases of habitual abortion; the abnormal width of the internal os may be the cause of the abortions in some of these cases.

The isthmic mucosa very rarely showed an abnormal pattern. Wherever it was observed, the outlines of the mucosa usually showed very characteristic changes consisting of crypts and duct-like projections. The past histories in almost all these cases revealed that the patient had had one or several curettages. This observation led to the assumption that the irregular pattern of the isthmic mucosa might have been caused by endometriosis. Large fistulae in the region of the isthmus were found only in very few cases. It was felt that they were the roentgen signs either of an existing tuberculous infection of the cervix and isthmus or of one that had healed.

Autoreview.

TOPOGRAPHISCHE AUSDEUTUNG DER BRONCHIEN IM RÖNTGENBILD MIT BERÜCKSICHTIGUNG DER NEUZEITLICHEN NOMENKLATUR. Von Claus Esser. 152 Seiten, 77 Abb. Fortschr. Röntgenstr. Ergänzungsband 66. Georg Thieme Verlag, Stuttgart 1951. DM 33: —.

The book consists of two main parts covering the general and special topography of the bronchial tree. In the general part the earlier anatomic and roentgenologic examinations of the bronchi are discussed. From them and the author's own roentgenologic investigations the nomenclature and formation of the bronchial tree with its different variations are discussed. Roentgen diagnosis of the bronchial pattern is dealt with in a special chapter. Bronchography, tomography and roentgen surveys are briefly touched upon without the author going further into the technique of such examinations.

In the special part of the book, the larger bronchi and their ramifications are considered separately. The writer deals systematically with each bronchial branch and explains 1) the various nomenclatures used 2) its origin 3) variation 4) course 5) qualities 6) relation to bloodvessels 7) how, in his opinion, it is best represented roentgenologically 8) its ramifications and 9) the area of the lung supplied.

The book deals in great detail with the variations of the smaller bronchi while deviations in the course of the larger bronchi are discussed with somewhat more restraint. The considerable displacements in the position of the bronchi which occur with large atelectases of the lungs are also treated rather briefly. The importance of selective bronchography is stressed.

The chief value of the book seems to consist in its use as a good reference work for the orientation of the different anatomic variations of the bronchi.

B. S. Holmgren.